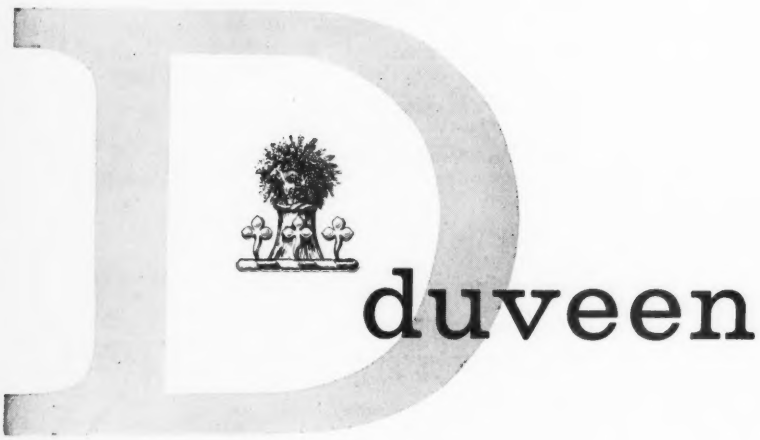

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Drug and Cosmetic Industry

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Keeping Posted

Six Month Sales and Earnings

Abbott Laboratories world sales for the first six months of 1960 were $62,208,000, compared with $58,448,000 in the same period of 1959, an increase of 6.4 per cent. Earnings rose to $5,810,000, compared with $5,584,000, an increase of 4.0 per cent.

American Hospital Supply Corporation reported that sales and earnings in the first six months of 1960 established new highs. Sales of $45,967,000 were 22.4 per cent greater than in the same period of 1959 when the figure was $37,564,000. Net earnings were $2,017,000, an increase of 18.4 per cent from the previous $1,704,000.

Cutter Laboratories, Inc., for the first six months of 1960 reported sales of $11,628,000, compared with $10,800,000, a 7.7 per cent increase. Net earnings in the same periods declined to $540,000 from $564,000.

Max Factor & Co. sales for the first half of 1960 reached a record high of $27,269,000, an 11.5 per cent increase over sales of $24,454,000 for the same period of 1959. Net profits declined from $1,770,000 to $1,638,000.

Hudson Vitamin Products, Inc., earnings for the fiscal year ended May 31, 1960 increased 85 per cent over the previous year and sales increased by 45 per cent. Corresponding dollar values were income of $987,000, compared with $534,000 while sales were $7,349,000 compared with $5,052,000.

Johnson & Johnson consolidated domestic sales of $154,211,000 for the first six months of 1960 were 2.9 per cent greater than the $149,892,000 reported in the first half of 1959 while earnings were $7,959,000, compared with $7,705,000. Net earnings of foreign operations for the first half of 1960 amounted to $2,294,000, compared with $2,347,000 while sales increased by 13.6 per cent.

Consolidated sales of *Eli Lilly and Company* for the first six months of 1960 were $91.1 million, compared with $94.1 million in the 1959 period. Net income in the same periods declined from $12.0 million to $10.9 million.

Sales of *Merck & Co., Inc.*, for the first six months of 1960 were slightly higher than in the first half of 1959, $111,416,000 against $110,787,000. Corresponding net income was $14,784,000, 6.7 per cent less than the $15,847,000 in 1959.

New records were set by *Norwich Pharmacal Company* for the first half of 1960. Sales were $21,377,000, 18.3 per cent higher than in the same period of 1959, while net income increased by 19.3 per cent to $2,473,000 from $2,071,000.

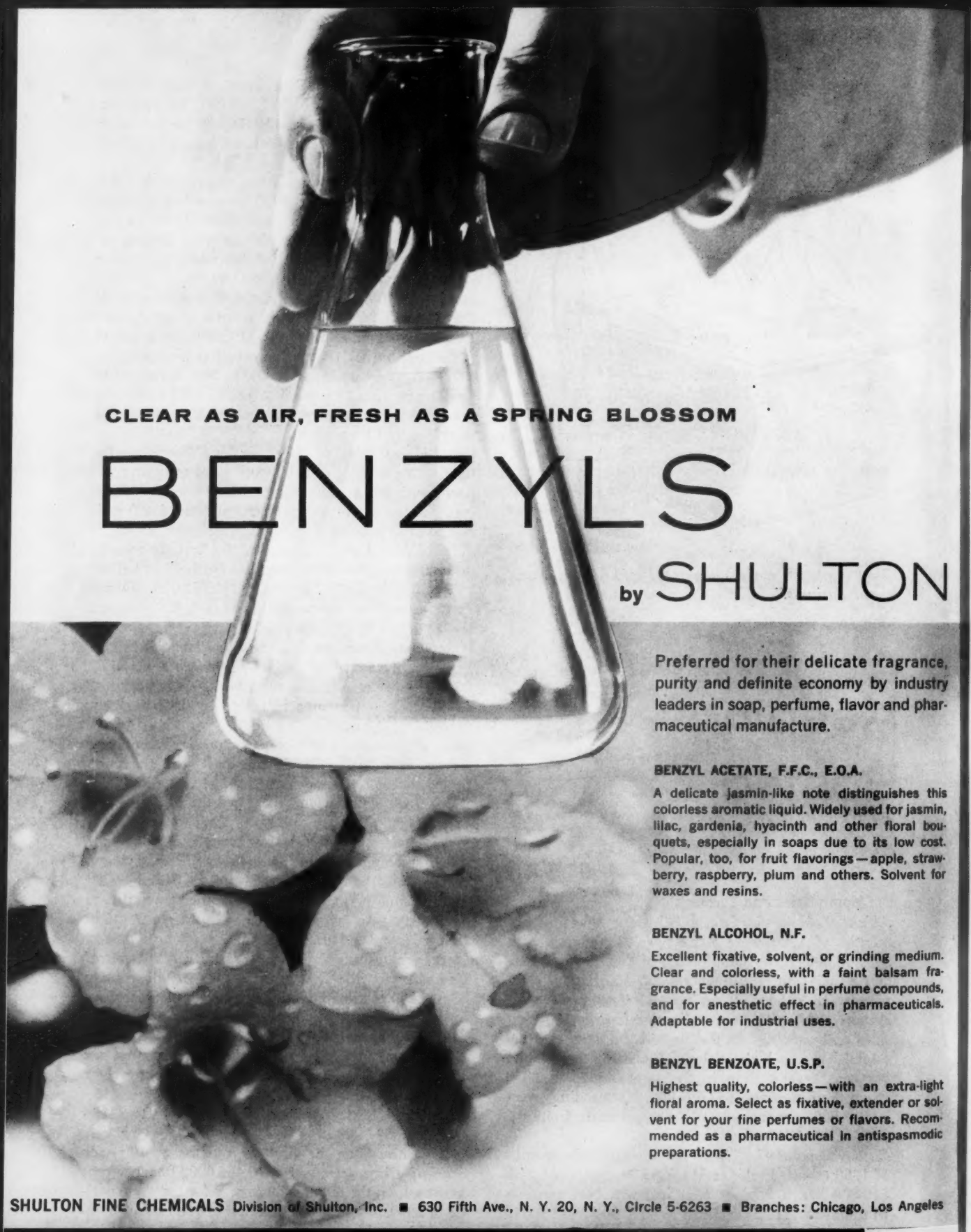
Olin Mathieson Chemical Corporation, reporting for the first half of 1960, compared with the same period of 1959, had sales of $348,281,000 and $347,296,000 while net income increased from $17,504,000 to $18,666,000.

World-wide sales of *Chas. Pfizer & Co., Inc.*, for the first half of 1960 amounted to $136,820,000, a rise of more than 11 per cent from the $122,899,000 for the same period last year. Earnings amounted to $12,900,000, an increase of 13 per cent from the 1959 first-half total of $11,397,000.

Net earnings of the *Rexall Drug and Chemical Company* for the first six months of 1960 rose to $3,638,000, compared with six-month net earnings in 1959 of $3,254,000. Sales for these periods were $112,307,000 in 1960 and $97,744,000 in 1959.

Consolidated net sales of *Shulton* for the first six months of 1960 were $18,028,000, 15 per cent greater than sales for the first half of 1959, which were $15,677,000. Net earnings increased 6 per cent to $818,000, from $771,000.

Net earnings for the first six months of 1960 for *Sterling Drug, Inc.*, were $10,467,000, 10.1 per cent greater than the $9,509,000 earned for the same period of 1959. Sales for the first half of 1960 were $110,661,000, an increase of 7.6 per cent over $102,840,-



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Sales of *The Upjohn Company* for the first half of 1960 totaled $76,486,000, an increase of 6 per cent over the $72,270,000 reported for the corresponding period in 1959. Earnings also increased by 7 per cent, from $9,814,000 to $10,510,000.

Vick Chemical Company sales for the fiscal year ended June 30, 1960 were $132,000,000, 14.5 per cent over the previous year's sales of $115,228,000. Earnings increased 17.2 per cent, from $12,157,000 to $14,300,000.

Warner-Lambert Pharmaceutical Company net income for the first half of 1960 was $7,466,000, compared with $6,733,000 in the corresponding period of 1959. Consolidated sales were $97,958,000 compared with $87,607,000.

Citric Acid Plant in Israel

Miles Chemical Company is to build a $2 million fermentation citric acid plant in Haifa, Israel. The plant will have a capacity of 1,500 short tons, 50 per cent of which will be for internal consumption, and the other half for export. The plant is to be built on a ten-acre site overlooking the Kishon River and will enable Israel to become a world leader in production of citric acid, according to Miles Chemical's president H. F. Roderick.

The all-Israeli operation will be controlled by Miles Chemicals Israel Ltd., a new subsidiary of Miles Laboratories. Directors will include Miles Laboratories president Walter R. Beardsley, Mr. Roderick, and Yaacov Salomon, Israeli attorney. Israeli technicians will be flown to Elkhart, Indiana, home of Miles Laboratories, for an extensive three-month training course, after which Miles intends to backstop the Israeli operations with "whatever technical assistance is needed during the start-up and production."

A share of the financing for the project was secured through a loan from the Government of Israel. The agreement was signed by Mr. Roderick and Pinhas Sapir, Israel's Minister of Commerce and Industry. In addition to the $3.6 million citric acid plant in Elkhart, Miles has a plant nearing completion in Mexico being built by a group of Mexican investors in partnership with Miles. This plant is scheduled to be on stream early in 1961.

Philips Expands in Pharmaceuticals

Chemico Laboratories, Inc., Miami ethical pharmaceutical manufacturer, has been bought by Philips Electronics and Pharmaceutical Industries Corporation, which company bought Columbus Pharmacal Company, of Columbus, Ohio, and last year merged with the Anchor Serum Company, of St. Joseph, Mo. The drug companies have been acquired by the Philips subsidiary, Philips Roxane, Inc.

Chesebrough-Pond's-Northam Warren

Purchase of the world-wide interests of Northam Warren and its affiliates by Chesebrough-Pond's, Inc., has been agreed upon by their boards of directors. The amount of cash involved was not disclosed but was estimated by some at close to $10 million. Northam Warren will be operated as a separate division. The company offers Cutex and Peggy Sage manicure products, Odorono deodorant, and Keenedge cutlery. There are 187,843 shares outstanding. Net income in 1959 was $1,103,119 or $5.87 a share. Assets total $9,191,268. The company has 700 employees and a plant at Stamford, Conn.

Chesebrough-Pond's assets total $39,768,383. Earnings for 1959 totaled $4,030,004, or $7.02 a share on 585,071 common shares. Sales totaled $66 million. The company has plants at Clinton, Conn.; New York, N. Y.; and Perth Amboy, N. J. Products are Pond's beauty preparations, Vasoline, petroleum jelly and hair tonics, Lipice pomade, Petrolatum gauze, Prince Matchabelli prefumes and men's toiletries, Seaforth men's toiletries, Simonetta perfumes, Aziza eye cosmetics, Pertussin cough syrup, lozenges, and vaporizers.

Northam Warren has announced his intention of retiring on December 31, but said he would continue in a consulting capacity. It is expected that the Northam Warren management under the leadership of Northam Warren, Jr., will continue to operate under present policies.

T.G.A. Favors Fair Trade

The Toilet Goods Association's board of directors went on record last September 29, as favoring the principles of price maintenance. This reverses the previous position of the Association, which in the past has taken no position on fair trade. A special committee was appointed under the chairmanship of Oscar Kolin, vice-president of Helena Rubinstein.

Declining Dihydrostreptomycin Market

The number of makers of dihydrostreptomycin has declined to three. These are Merck, Pfizer, and Squibb. Lederle gave up production of the drug about a year ago, being discouraged with low prices and over-production. Now Eli Lilly and Company no longer offers the drug for human use, although it continues to supply veterinary markets from existing stocks. The $13 million market for the drug is not considered very stable as the result of the Food and Drug Administration's proposed changes in labeling requirements. These require manufacturers to give warning of possible impairment of hearing, which has been known to follow repeated large doses of the antibiotic.

Before the announcement of the FDA last month, it was clear that the trend was away from dihydrostreptomycin to streptomycin. Output of dihydrostreptomycin fell from 581,000 pounds in 1958 to 470,000 pounds in 1959, while production of streptomycin rose from 179,000 pounds in 1958 to 281,000 pounds in 1959. Also exports of dosage forms of dihydrostreptomycin dropped from 20,344,755 grams

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in 1958 to 12,082,999 grams in 1959, while exports of streptomycin dosage forms rose from 37,946,143 grams in 1958 to 56,133,547 grams in 1959.

The prices for dihydrostreptomycin have been declining for the past four months or more. This is said to reflect the fact that the market for the drug today is almost completely in veterinary medicine. However, it is thought in veterinary medicine a sharp switch will also take place from dihydrostreptomycin to streptomycin.

Because of the likelihood of dihydrostreptomycin causing delayed deafness, FDA has required that producers state in the labeling that frequent auditory and caloric tests should be performed on all patients receiving the drug on a long-term basis. The latest information indicates that the danger to the patient's hearing is greater than first suspected. FDA says that auditory impairment or total deafness can result from a much smaller dose and over a shorter period of time than was formerly believed necessary to produce the injury.

This situation, in addition to the criticisms before the Kefauver Committee over the Summer, has forced FDA to change the labeling requirements. The proposal is that the following warning should appear on outside wrappers, as well on the immediate containers themselves:

"Warning: For use only in patients who cannot tolerate streptomycin" (for dihydrostreptomycin sulfate and for dihydrostreptomycin solution). Or "Warning: For use only in the treatment of patients who cannot tolerate full doses of streptomycin" (for mixtures of dihydrostreptomycin and streptomycin). Also to be included in the warnings will be information that because of its potentiality for causing delayed deafness, dihydrostreptomycin sulfate should be administered only to patients having infections amenable to treatment with streptomycin or dihydrostreptomycin, but for whom streptomycin is contraindicated. In the case of mixtures of the two drugs, the labeling should limit the drug's use to patients having tuberculosis who are amenable to treatment with one or both of the drugs but who cannot tolerate full doses of streptomycin. In the case of all of these products, the labeling must state that severe auditory damage has been reported following a total parenteral application of as little as two to five grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months, the proposed warning concludes.

Fishbein's Medical Predictions

Dr. Morris Fishbein predicts that the next generation of physicians will see: (1) elimination of infectious diseases such as measles, scarlet fever, whooping cough, mumps, diphtheria, respiratory disorders, and poliomyelitis; (2) a population in which 20 per cent will be more than 65 years of age, and 2 per cent over 100 years; (3) virtual elimination of physical and mental handicaps.

In an address before 200 doctors attending the dedication of Irwin, Neisler & Co. research laboratory, Dr. Fishbein warned that the next generation will have to combat "flash epidemics" of imported infections as long as these diseases exist elsewhere in the world. Our own population will lack the immunities which older generations have acquired by casual exposure and will be extraordinarily susceptible. Medicine will have to organize "diaster teams" to handle these epidemics to enforce quarantines. These teams will also hospitalize and treat the ill with bactericides and viricides, fortify the exposed with vaccines, and perform all other mopping up operations that may be found necessary to wipe out the infections.

Geriatrics will become very much like pediatrics, said Dr. Fishbein. Control of enzyme systems within the body will stave off degeneration of the blood vessels and heart, the edocrine glands and other organs, which produce aging. The time of life which will be regarded as "old age" will continue to rise, as it has in recent decades, because persons in their seventies and eighties will be still vigorous and capable of living joyful, productive lives.

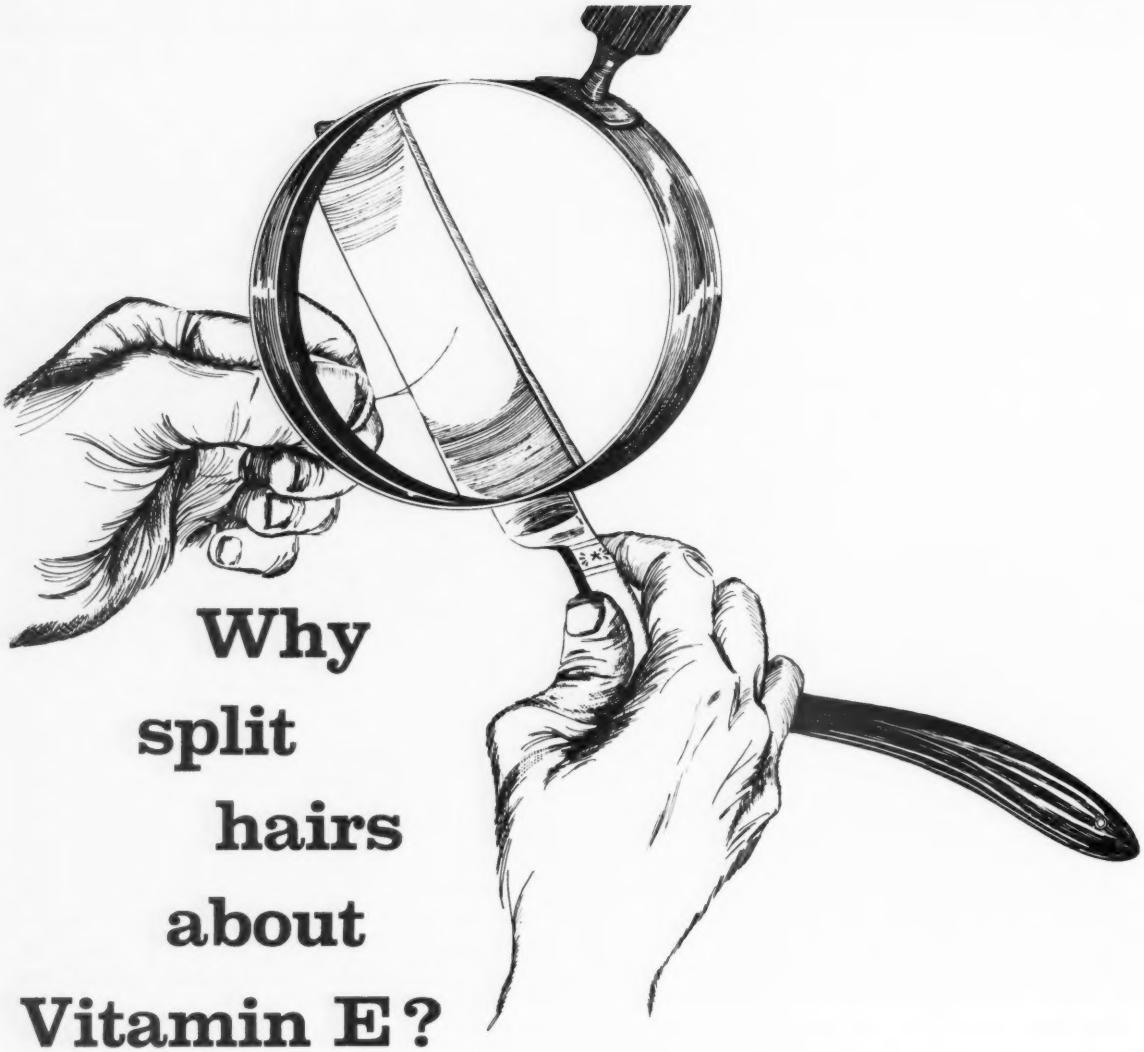
Mental retardation, which now afflicts approximately 3 per cent of the population will tend to disappear as new research findings on the processes of learning are applied to child training in the school and, even more importantly, in the home during infancy.

Heart and blood vessel diseases, cancer, and other degenerative conditions will be ameliorated by better drugs and better use of surgery and such physical forces as light, heat, and electricity.

Kefauver Committee and Antibiotics

Witnesses before the Senate Antitrust and Monopoly Subcommittee (Kefauver Committee), resumed hearings last month to discuss antibiotics. The first witness was Dr. W. G. Malcolm, president of American Cyanamid Company, who described Lederle Laboratories Division of the company, saying that ethical drugs constitute more than 90 per cent of their human drug products and account for more than 95 per cent of their sales. Lederle has more than 325 drugs in finished form, and most of their sales today come from products not known ten years ago.

Lederle was transformed in 1939 from a traditional biological house and, along with this fundamental change, the company adopted a pricing policy based on the great risk and continuing high costs of a business of this kind. Therefore, the company tries to achieve an over-all profit margin for Lederle of 12 to 15 per cent on net sales after taxes. Profits were slightly in excess of 15 per cent for the last two or three years, but this is considered too short a period to justify the adjustment of prices. Profits rose as high as 19 per cent in 1950, but declined to 11.6 per cent in 1952, and the average since 1939 has been 14.1 per cent.



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Dr. Malcolm described the promotional and selling activities of Lederle. In a typical month, Lederle spent $1.65 in promoting the sale of drugs to each of the country's 200,000 practicing physicians, and $1.86 in advertising drugs to each. Of the money spent on promotion, $1.33, or approximately 80 per cent, was spent on samples to enable the doctor to observe the drug personally. Of the money spent on advertising, $1.06 went to medical journals, and 52 cents per doctor was spent on direct-mail advertising. He spoke of the support which each of the 800 medical journals published in the United States receives through drug advertising.

All advertising is subject to the absolute veto of the medical director, whose decision has never been overridden. Each of the accredited medical schools in the United States and Canada receives a Lederle grant yearly to help students devote Summer vacations to research.

Dr. Philip Bowman, president of Bristol Laboratories, read a 30-page statement. He told of Bristol's growth from its small start, of the purchase of the assets of the $255,000 company in 1943, compared with Bristol's $23.5 million assets and net after taxes of $2.17 million on sales of $25.8 million. He stressed the fact that a great amount of money was spent on research and that patents had given the company a chance to grow. He told that, despite the losses in the 1944 to 1953 period, the company continued with its research. He said it is possible for a small company to enter and survive in the drug industry, but it must be prepared to spend at least 9 per cent of sales on research and must have patent protection. He said his company had averaged 12 per cent on research during its corporate lifetime, and had put almost two dollars into research for every dollar realized in profit.

Harry J. Loynd, president of Park, Davis & Company, testified without a prepared statement but did have a statement to show his company's over-all cost of doing business, against the 27.5 cents it gets for a capsule of Chloromycetin.

Eugene Beeseley, president of Eli Lilly and Company, said that his company's patent licensing policy is flexible. He said Lilly has received 65 patents in the antibiotics field, some of which have been licensed and others have not. Last year the net income was 10.9 per cent of assets, and a further decline to 8.6 per cent is estimated for 1960. Lilly, he said, was a major contributor to the discovery and development of antibiotic medicines, and has taken great risks to develop facilities. Of the company's total United States investment in fixed assets, 40 per cent relates to antibiotics, which produce 25 per cent of the company's sales.

Florida's Drug and Cosmetic Registration

The State of Florida has enacted a bill which requires registration of drugs, cosmetics, and devices, as well as food products, under the Florida State Board of Health. This legislation is an amendment of Chapter 500 of the Florida Food, Drug, and Cosmetic Act. The amendment becomes effective January 15, 1961, and sale on or after that date of any product not registered is illegal. Blanks for registration are already being sent out by the Florida State Board of Health. The cost is $2.50 per product, but there is an over-all fee of $25 for registration of more than ten products.

Registrations made for January 15, 1961, will expire on June 30, 1961, and must be renewed on July 1 of each year ". . . provided, that if any person who is subject to the requirements of this section shall fail to comply herewith by August 1 of any year the Board of Health shall have the authority to issue a stop-sale notice or order against such person . . ."

Virus Linked With Eight Cancers

A virus has been linked with eight human cancers in findings reported by scientists at the Sloan-Kettering Institute for Cancer Research, New York. The virus was isolated from transplanted tumors of the mouth, muscle, ovary, and other tissues, and from the noncancerous livers and spleens of cancer patients.

Before this report, the only human cancer stated to have been associated with a virus was leukemia. Therefore, this latest report adds considerable weight to the growing speculation that a wide range of human cancers may be virus-caused. Whether viruses have caused any of the human cancers with which they have been associated is not yet known, and considerably more research must be conducted before this is definitely known. Should it be found that viruses produce malignancy in humans, as they have been found to in many plants and animals, important new avenues of attack on the disease would be opened.

It might be possible to develop vaccines for prevention of cancer, possibly only a single vaccine against several manifestations of the disease. Also, if scientists find a way of combating virus with drugs, cancer would become vulnerable to chemotherapy. Another possibility is that sensitive tests could be devised for detecting virus-caused tumors that might otherwise escape notice until too late.

Measles Vaccine Test by New York City

A five-year test of a new measles vaccine on children on Staten Island, New York City, and in Nigeria, is to be undertaken by the New York City Health Research Council. An expenditure of $159,885 was approved for the project. The vaccine was developed by a Boston group under Professor John F. Enders of Harvard Medical School. Dr. Enders produced the vaccine by attenuating it through a long process of growth in successive cultures of chick embryo cells. Laboratory experiments and preliminary trials in five cities, including New York, have produced results described as "very encouraging" by Dr. Saul

Krugman, chairman of the Department of Pediatrics of the New York University Medical Center. Dr. Krugman, who is in charge of a team of N.Y.U. scientists that will conduct the test, will leave for Africa on November 11. The Staten Island tests are already under way. The vaccine will be given, with parental consent, to 1,500 children at the Willowbrook State School, an institution for retarded children, and to 4,000 children in Nigeria. After the five-year program is completed, an even broader series of trials will be necessary before the vaccine can be released to the public.

PWA Offers Associate Memberships

The Pharmaceutical Wholesalers Association is now offering associate membership to the pharmaceutical industry. Applications for pharmaceutical companies to join have been sent to leading companies with a letter from Carroll G. Waterman, president of the PWA, which states:

"The concept that led to the founding of an association of such wholesalers is now spreading; and, from information coming to our Association, I feel that it will not belong before every section of the country will benefit from the service of a pharmaceutical wholesaler . . . An Associate Membership will enable your company to keep abreast of new developments in pharmaceutical distribution and to take advantage of consequent changes."

PWA was founded on the West Coast in 1956, and now has members as far east as St. Louis, and an eastern office in New York. Member firms handle ethical prescription drugs, which are made available to the pharmacist "through efficient and immediate service."

Baxter Building in South Carolina

Baxter Laboratories, Inc., has started building a new 92,000 square-foot plant on a 47-acre tract near Kingstree, S. C. The plant, which will employ approximately 100 people, will manufacture intravenous solutions for hospital use, blood equipment and pharmaceutical specialties. This plant will give Baxter a location on the Eastern Seaboard; it will put the company in a good position for the growth that has already taken place in that area and also for the future growth that is anticipated, it is said. Manager of the Kingstree plant will be Donald C. Madsen, who for the past six years has been manager of Baxter's plant in Brussels, Belgium.

Burroughs Wellcome Plant Addition

Construction, which is beginning to look like an old-fashioned obstacle race, has begun as a five-story addition to the manufacturing building of Burroughs Wellcome & Co. at Tuckahoe, N. Y. The addition is being built to permit the lengthening of production lines in a 40-year-old building.

With studies beginning last year by the designer and builder, the project has turned into one of the most complex of its kind, due to a number of factors over which the owner or the builder could not exercise control, and it illustrates the great lengths to which industry must go to expand its facilities in land-scarce suburbia.

The new addition starts at the north side of the manufacturing building and measures 71 by 113 feet. But located on the site of the proposed structure were two existing buildings: a one-story machine and equipment shop, and the main boiler house, which recently had been modernized with new steam generators.

Since the machine shop could not be demolished until new space was readied for it in the new addition, and because the boiler house and its new equipment was to be partially incorporated into the new structure, the builder had to build the new structure in, over, and around the two smaller units. This called for extreme delicacy in foundation and steel work. Silty soils overlaying irregular rock below the river bottom made it necessary to install caisson-piled foundations throughout the engine room and boiler house, and holes had to be punched through the boiler room walls and roof to allow for setting of structural steel members. Because the ceiling height of the engine room, which was to become part of the new addition, was not at a permissible level with the main manufacturing building, a new ceiling had to be constructed inside the structure and the old roof sliced off. During all this time, steel work erection was obstructed by existing equipment and piping in the boiler house and machine shop. The builder had to surmount this with an elaborately cantilevered framework to carry the weight of the building down to its underpinnings.

Several old sewage and drainage lines were found under the site and had to be relocated. On top of that, test borings uncovered existing foundations—some, seven feet thick—from an earlier structure demolished years ago. These had to be cut through before the ten- to 20-foot supporting caissons could be sunk. The deep foundations were made necessary because of the jagged contour of the rock below with its steeply sloping surfaces. However, the project will be finished on time this year.

Vick Research Increases

Vick Chemical Company, or Richardson-Merrell, Inc., spent $4,800,000 on research in the fiscal year ended June 30, 1960, triple the amount spent five years ago. This amount will be increased 15 per cent for the current year. MER/29, a new drug developed by Merrell research to regulate the body's own production of cholesterol, is now selling at a higher current rate than any of the company's other ethical products. Introduced June 1, 1960, the number of prescriptions written was very high. Also the rate of sales increased each month, and prescription surveys show five out of seven prescriptions are being refilled—a very high ratio.

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RAW MATERIALS AND PRODUCT QUALITY

BY JEAN R. L. MARTIN MARTIN - VALER, CONSULTANTS

From time to time our consulting firm is given various cosmetic and pharmaceutical preparations for appraisal and investigation. It always astonishes me to find, in a trade where so much money is spent on advertising, promotion, and presentation, that the quality, appearance, or odor of so many of these products is often not good enough, or at least not as good as could be expected. This is all the more astonishing because, in most cases, a little extra work and care would remedy the deficiencies, transform a mediocre preparation, and improve it generally. We wonder what the cause may be. Does it stem from a lack of fastidiousness or artistic sense on the part of the formulator or, rather, from a near-sighted, penny-pinching philosophy?

Given today's retail prices for cosmetics, is there any reason, for instance, to use (as we have seen it) tap water, which is rarely clean, usually smells of disinfectants and can play havoc with the odor and composition of the formula, instead of deionized water, which costs fractions of a penny per gallon? Is there any reason, except in a few instances, to use isopropanol instead of ethanol and, by saving a few cents per gallon of alcohol, spoil the ultimate odor of otherwise acceptable products? Is there any reason to use second-rate raw materials and with them prepare products of impaired color, odor, and quality? And is it logical and fair to present the perfumer with such preparations, when doing so complicates unnecessarily his already difficult and complex task?

This problem is, of course, not new. A few years ago, this very subject, as seen from the perfumer's side, was discussed by Dr. Oliver Marton, chief perfumer of Shulton, Inc., at a symposium of the American Society of Perfumers. He practically begged the cosmetic chemists to think of the perfumers' problems and to cooperate by giving them products as odorless as was compatible with their performance. I fully agree with Dr. Marton, because this kind of team work lead to improvements and better cosmetics.

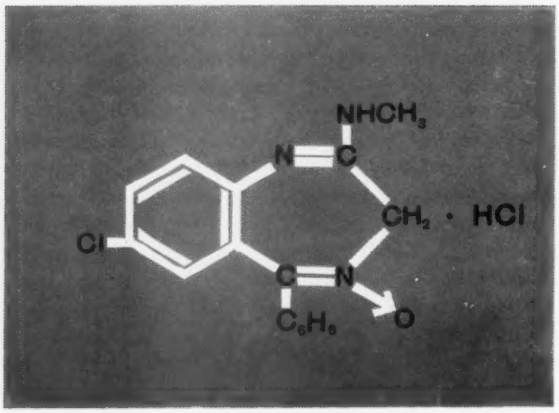
Against this view, two arguments are often presented, the first usually from manufacturers of pharmaceutical products. They claim that the public links performance with medicinal odors such as phenolics, camphor, and—in the case of lanolin ointments—to a definite sheep odor. They are of the opinion that if these odors are disguised, customers will lose confidence.

I do not find this argument very convincing. It is possible that a few users will complain but, since people are becoming more and more odor conscious, it is more than likely that the majority will be

(*Continued on page 530*)

LIBRIUM
A Marketing Case History

BY MILTON MOSKOWITZ



In 1955, there were three pharmaceutical companies marketing three tranquilizer products.

By 1957, there were ten companies in the field with 13 tranquilizers.

Last year, 19 companies were marketing 27 tranquilizers.

These companies divided up a market that had expanded in six years from zero to $150,000,000 (at manufacturers' prices).

This year, there was a new entry in the field—Librium—marketed by the Roche Laboratories division of Hoffmann-La Roche, Inc., Nutley, N. J. New products have been the lifeblood of the pharmaceutical industry and Librium's impact on the tranquilizer market shows why.

Three months after its introduction in March of this year, Librium had become the most prescribed tranquilizer in the nation. Its sales mounted steadily month by month so that by the time September arrived—six months after its introduction—Librium's volume was running at the annual rate of $24,000,000 ($2,000,000 a month), giving the Swiss chemical and pharmaceutical house a 16 per cent share of the entire tranquilizer business in the United States.

This is, of course, a sensational showing for a new product, and the elements that added up to Librium's success deserve some examination.

First of all, one must look at the general background of the tranquilizer market. Nonbarbiturate tranquilizers, or ataraxics, first appeared on the market in 1954 in the form of the rauwolfia derivatives, and chlorpromazine, marketed by Smith, Kline & French Laboratories as Thorazine. They were soon followed by meprobamate, developed by the Wallace Laboratories division of Carter Products Inc. Wallace marketed meprobamate as Miltown, a brand name that rapidly became a household word in America. Wallace, a company with no sales force, licensed Wyeth Laboratories division of American Home Products to market meprobamate as Equanil.

These new drugs revolutionized the treatment of mental illness. Their use in mental hospitals resulted in the release of thousands of psychotic patients. Many disturbed people became accessible, for the first time, to psychoanalytic therapy. In addition, the tranquilizers became a favorite tool of the general practitioner in treating mild anxiety among his patients.

These new drugs also revolutionized the sales of the three kingpins of this new market—SK&F, Wallace, and Wyeth. Suffice it to say that *all three* have doubled their sales since the introduction of tranquilizers.

Tranquilizer sales rose steadily until 1958, when they leveled off at about 20,000,000 new prescriptions a year, or a little more than 5 per cent of all new prescriptions. There has been considerable jockeying for position in this market.

In 1955, the first full year of tranquilizer marketing, Thorazine captured two-thirds of the entire business.

In 1957, when Miltown was all the rage, the meprobamates did one-half of the business; Thorazine had been reduced to 12 per cent of a much bigger market while other phenothiazines, principally SK&F's, held 22 per cent of the market.

In 1959, the phenothiazines (now available in milder forms) advanced to the top again with 48 per cent of the market, compared with meprobamate's 38 per cent. SK&F's three top-selling phenothiazines —Compazine, Thorazine, and Stelazine—enjoyed about 30 per cent of the entire business. At the top of the heap, with estimated sales of $35,000,000, was

NEW PRESCRIPTIONS OF TRANQUILIZERS IN 1960

	January	March	April	June
Librium	———	60,000	200,000	320,000
Equanil	375,000	300,000	300,000	275,000
Compazine	300,000	290,000	260,000	180,000
Thorazine	150,000	150,000	130,000	100,000
Miltown	140,000	125,000	120,000	115,000
Stelazine	125,000	120,000	110,000	120,000

Wyeth's Equanil, which has consistently outsold Miltown (a reflection of the doctors' confidence in the Wyeth name, since the two products are identical).

Now, enter Librium. Before putting this product on the market last March, Roche Labs had every indication that it had a winner on its hands. These indications came from extensive clinical trials stretching over two years. Thus, before a single prescription for Librium was written, Roche was able to point out that the new drug had been tested by nearly 2,000 physicians in treating some 20,000 patients, had been "employed in more than half the accredited medical schools of the country," and had been "the subject of 17 published reports."

These pre-market trials provided Roche with the ammunition it needed to invade this highly competitive market. New pharmaceutical products are introduced at the rate of 400 a year and all of them go through clinical testing before being introduced. Few of them, however, emerge from these trials with the established claim to "a unique product, different from all others that came before." This was the case with Librium.

A good many of the new drugs introduced in the course of a year are variations of older products, often achieved by altering molecular structures. These alterations can, of course, result in improved products. In Librium, however, Roche had an entirely new chemical agent, synthesized in its New Jersey laboratories by Dr. L. Sternbach. Roche could point out to doctors that Librium was "not a manipulated molecule."

Librium's efficacy as a tranquilizing agent received striking corroboration during the field tests. It was found to have what one physician called "a unique taming effect," in that it freed the patient from anxiety and tension "without reducing mental alertness, dulling the senses or decreasing perception." Since the principal objection to the tranquilizers had been that they tranquilized the patient into a state of drowsiness, this was a key finding.

The clinical tests also showed that Librium had application in cases "ranging from the mild to the moderately severe." This, too, was a key finding, since the tranquilizers previously had divided into two types—meprobamate for mild anxiety and tension, phenothiazines for severe emotional disorders.

Emboldened by these findings, Roche mapped out a marketing program designed to hit not just a segment of the market but the entire tranquilizer market. It took as its target every other tranquilizer on the market. This was admittedly risky; Roche recognized that "any attempt to aim at both halves of the market entailed a risk of failing to capture either."

Dr. V. D. Mattia, general manager of Roche Labs, assumed responsibility for the marketing program, along with William Gulick, director of advertising. Advertising itself was assigned to William Douglas McAdams Inc., ethical drug advertising agency.

Roche began advertising Librium in March, using the three traditional media of pharmaceutical marketing—detailing, medical journals, and direct mail. Detail men left with doctors the Roche Record Report, a promotional booklet containing five long-playing records on which physicians reported the results of Librium therapy. Imposing eight-page inserts ran in leading medical journals. In the mail, doctors began receiving informational reports on Librium, the first of a series of 40 mailings Roche scheduled from March to July.

It takes a substantial investment to introduce a major new product in today's ethical drug market. Roche will be spending a minimum of $2,000,000 to advertise Librium in 1960. Ads are scheduled in some 45 medical journals and doctors are being hit with more than five mailing pieces a month. Roche's sampling costs are low because, unlike many members of the industry, it has no great belief in free samples as an effective promotional tool.

Librium's advertising campaign has attracted wide attention in the industry. Geared to capitalize fully on the advance clinical findings, the campaign sought from the start to isolate Librium as a drug "in a class by itself." This posed difficulties. All new drugs are introduced today with so much hoopla that doctors tend to discount many of the promotional claims. Roche therefore decided that its best bet was "to underplay an essentially very strong hand." The opening shot in the campaign thus featured this relaxed sell:

"At this time, Roche Laboratories introduces a new psychopharmacologic agent: Librium. [In other words, another tranquilizer?] Another tranquilizer, yes, in a manner of speaking. That is, insofar as it allays anxiety, tension and agitation, Librium could perhaps be called a tranquilizer (we see no point in coining a new, fanciful descriptive term). But Librium has several noteworthy properties that distinguish it from any 'tranquilizer' you ever heard of or used . . . and it is very definitely *not* just another addition to an already lengthy list. [Isn't that a rather familiar claim?] Perhaps. In this message, however, we would like to transmit to you our own profound conviction that Librium *deserves* to be made available to the medical profession—despite (or possibly because of) the existing compounds—and to let you share the enthusiasm of the many investigators (some of whom originally approached Librium with a certain degree of skepticism). [What is Librium? When should it be used? What are its limitations? How does it fit into my practice?] Please read on. . . ." (*Continued on page 566*)

DIHYDROXYACETONE Synthetic Versus Natural Sun Tan

BY F. J. BANDELIN, VICE - PRESIDENT AND DIRECTOR OF RESEARCH, STRONG COBB ARNER INC.

Dihydroxyacetone has leaped to prominence in the past year because of its singular and unique property of reacting with the skin to give a reddish-brown color that simulates, in most instances, a natural sun tan. The compound has been used cosmetically in various solutions, creams, and lotions, for topical application to produce the tan stain that develops from three to six hours after application.

The remarkable aspect of this situation is that the compound has long been known as a chemical entity, but its skin tanning property is a fairly recent discovery.

Physically, dihydroxyacetone is a white crystalline powder, somewhat hygroscopic. Cryoscopic measurements indicate that dihydroxyacetone is a dimer. By either melting or using heat to effect solution in a solvent, the monomer can be regenerated from the dimer. Reversion to a monomer is rapid in aqueous solutions when using freshly prepared dihydroxyacetone; it slows down as the age of the dimer increases.

The solubility characteristics are dependent upon the dihydroxyacetone molecular arrangement form, monomer or dimer. The monomer is very soluble in cold water, alcohol, ether, or acetone, the dimer is only slightly soluble in cold absolute alcohol, ether, and acetone. The solubility characteristics of the monomer are obtained in these solvents by warming. Both monomer and dimer are insoluble in hydrocarbons.[1]

Chemically, dihydroxyacetone is 1,3 dihydroxy-2-propanone. Fischer, in 1888, used glycerose, a mixtrue of glyceraldehyde and dihydroxyacetone, as a starting material for sugar synthesis.[2] These apparently undergo aldol condensation with the formation of a ketose, which has the same formula as fructose. A mixture of glyceraldehyde and dihydroxyacetone may be obtained by the careful oxidation of glycerol. It can also be prepared from glyceraldehyde through the common enediol.[3]

Dihydroxyacetone is produced commercially by fermentation of glycerol. The remarkable property

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of bacteria of the genus *Acetobacter* in oxidizing a secondary alcohol group of certain sugar alcohols was first discovered by Bertrand,[4] who found that the organisms attack a secondary alcohol group on a penultimate carbon atom. This biological reaction is highly specific and efficient. According to Spector,[5] a fermentation mixture consisting of 5 per cent glycerine, 0.5 per cent yeast extract, at a temperature of 28 to 30° C. is converted to dihydroxyacetone with a yield of 90 per cent by *Acetobacter suboxydans*. Other species such as *melanogenum* have also been reported for the conversion.[6]

The compound may be considered as being physiological, since dihydroxyacetone-1-phosphate is one of the primary intermediates in the metabolism of glycerol and carbohydrates in microorganisms, plants and higher animals, and is present in the Kreb's cycle in the utilization of carbohydrates. Oral administration causes an increase in the lactic acid level of the blood.[7] Other metabolic pathways involving

dihydroxyacetone phosphate in glycerol, glyceraldehyde, in hexose diphosphate metabolism, and in the utilization of fats have been described.[8]

Dihydroxyacetone forms glycogen in the body more rapidly than glucose. This may occur directly or through intermediate conversion to lactic acid or one of the other three carbon glycogen precursors. Metabolic studies in man also show that it produces a more rapid elevation in respiratory quotient, greater heat production and greater oxygen consumption than glucose. It prevents excessive formation of beta hydroxy butyric acid and acetoacetic acid. It has been reported to be of value as a carbohydrate material for diabetics.[9-11] This, however, is somewhat doubtful. It has also been used as a respiratory stimulant.[12-13]

Being a relatively small, polyfunctional molecule containing two methylene groups, two primary alcohol groups, and a carbonyl group, dihydroxyacetone takes part in numerous reactions, including condensations and polymerizations. In addition, it is a ketotriose and undergoes many of the reactions associated with simple sugars.

The fact that dihydroxyacetone reacts with skin protein to produce colored end products is not surprising. Its affinity for protein and rate of reaction is, however, unanticipated. The interaction between carbohydrates and amino acids and proteins has gradually become recognized as a widespread, naturally occurring biological phenomena. The dark-colored products formed by the reaction of sugars with amino acids were extensively investigated by Maillard.[14-16] These dark substances of complex nature are called melanoidins.

The melanoidins are to be distinguished from the melanins, the black pigments found in plants and animals and the dark compounds formed by the action of oxidizing enzymes such as tyrosinase.

In natural products, the primary reaction occurring between sugars and amino acids or proteins is the condensation between amino, imino, or amide groups of the nitrogenous substance and the aldehyde or hemiacetal group of the sugar. The tautomeric forms in which sugars react are not known. The general types of reactions between amines and aldehydes have been reviewed by Sprung.[17] The usual type of reaction, the first stage of which is analogous to the aldol condensation of aldehydes, is the formation of Schiff bases:

$$\text{R-CHO} + \text{R'NH}_2 \longrightarrow \text{RCH(OH)-NHR'} \longrightarrow \text{RCH} = \text{NR'} + \text{H}_2\text{O}$$

Usually the alpha-hydroxy amine has not been isolated, for the reaction proceeds rapidly to the imine (Schiff base). Secondary amines undergo the reaction, but tertiary amines, unless part of an aromatic ring system, do not. Many aldehyde-amine products polymerize. Since polymerizations offer some clue to the mechanism of conversion of sugar-amine products into dark substances, this may be the mechanism of the dihydroxyacetone-protein reaction. Amino groups of the protein may react directly with the carbonyl of the dihydroxyacetone. Buchter, Bandelin, and Kanas[18] have investigated the color reactions of dihydroxyacetone with various amino acids and proteins, and found that glycine reacts most readily of the amino acids. They also found that the reaction with proteins to give yellow to dark brown products is more rapid than reaction with amino acids. With both amino acids and proteins, the reactions occur more readily without an excess of water. The amount of water required to produce reaction was that amount required only to moisten the dry powder. This seems to indicate that the color reaction is an adsorption, coacervation, and surface phenom-

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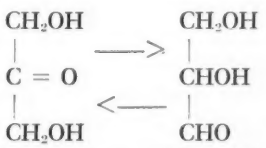
ena. These investigators also postulated that dihydroxyacetone may react in a tautomeric form through an aldehyde group on one of the terminal carbon atoms, possibly as glyceraldehyde.



Dihydroxyacetone Glyceraldehyde

Through this type of shift, it may be possible for glyceraldehyde and dihydroxyacetone to exist in tautomeric equilibrium. In this case, the Schiff-type reaction between the amino or imino groups of the proteins with the aldehyde group would better explain the rapidity of action and the apparent subsequent polymerization with the keratin to produce the brown coloration. These types of products are

(Continued on page 542)

DESIGN of Oral Sustained-Action Dosage Forms*

BY JOSEPH V. SWINTOSKY, Ph.D. SMITH KLINE & FRENCH LABORATORIES

I wish to discuss the following factors as they relate to sustained-action oral dosage forms:

1. The selection of a drug.
2. Theoretical and experimental approaches.
3. Preparation, and therapeutic effectiveness.

Factors Influencing Selection

Size of dose. One of the principal objectives of prescribing and dispensing drugs in sustained-action form is the convenience of less frequent drug administration. The product, then, must include in a single dosage unit the amount of drug normally given in several doses. Drugs that require low doses do not present special problems; drugs that require large doses may present some problems; drugs that require exceptionally large doses may not be suitable for incorporation in the usual sustained-action single dosage unit.

Safety considerations. Doses and dosage regimens must be selected and tested to assure that the product is useful therapeutically and free from serious hazard under recommended conditions for use. Tests for toxicity and for clinical safety must be applied as rigorously in the development of sustained-action products as for any other dosage forms.

Duration of action of usual dose. Certain drugs possess the intrinsic quality of long action. No appreciable benefits result from prolonging their absorption and action. For example, some of the digitalis glycosides have useful therapeutic effects that persist for long periods.[1] The present state of knowledge indicates that these drugs can be administered satisfactorily once a day without special attempts to prolong their action through formulation.

Absorbability in gastrointestinal tract. Some drugs appear to be absorbed at rates and efficiencies which are quite variable in different portions of the tract. For drugs that are absorbed in only a very small portion of the tract, the utility of a sustained-action product would be questionable.

It also appears that if a drug is not absorbed well from the tract when administered in the plain form, physiologic availability may be seriously suppressed when the drug release is protracted. Such drugs are questionable candidates for sustained-action dosage forms.

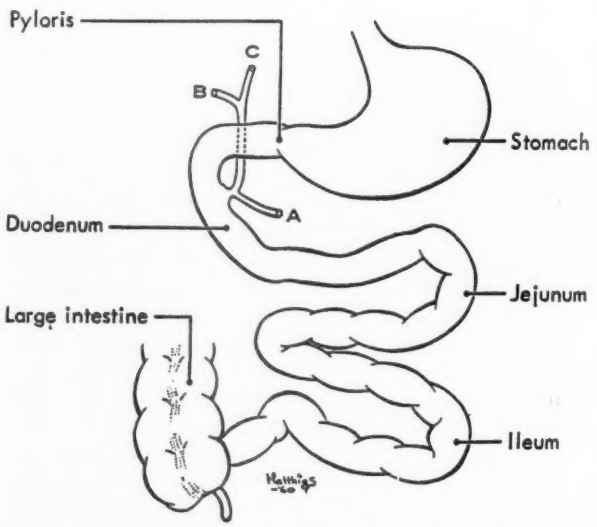


Figure 1. Schematic diagram of the digestive tract. Letters A, B, and C indicate, respectively, ducts leading from the pancreas, gall bladder, and liver.

Release integrity of products. Some drugs and some formulation techniques result in products that do not retain a desirable release pattern during storage. Changes in the release pattern may produce change in the product's efficacy. Therefore, suitable storage tests should be conducted on new products before marketing, to establish that they will retain a dependable release pattern.

Physiologic factors. Gastrointestinal physiology has a considerable bearing on the design and utility of sustained-action products, and warrants somewhat more detailed discussion than the preceding factors.

Figure 1 is a schematic diagram illustrating some pertinent features of the gastrointestinal tract. Solid particles entering the stomach may lie there for periods that can vary from a few minutes to several hours, depending upon a variety of conditions. Among other things, stomach fluid contains water, hydrochloric acid (usually at a *p*H between 1 and 4)

*Presented at the St. John's University Pharmacy Congress, Jamaica, N. Y., March 1960.

and the proteolytic enzyme, pepsin. The pyloric sphincter when closed prohibits movement of material from the stomach; when relaxed it permits the movement of substances from the stomach to the duodenum. Movement of solid particles into the region of the pyloric area stimulates the pyloris to close. The particles then, remain in the stomach and are acted upon by the stomach fluid. The action of the fluid may be enhanced by gastric motility.

Brodie, Hogben, Schanker, and associates[2-4] have demonstrated in laboratory test animals that a relationship exists between the dissociation constant and the rate and degree of absorption of acidic and basic

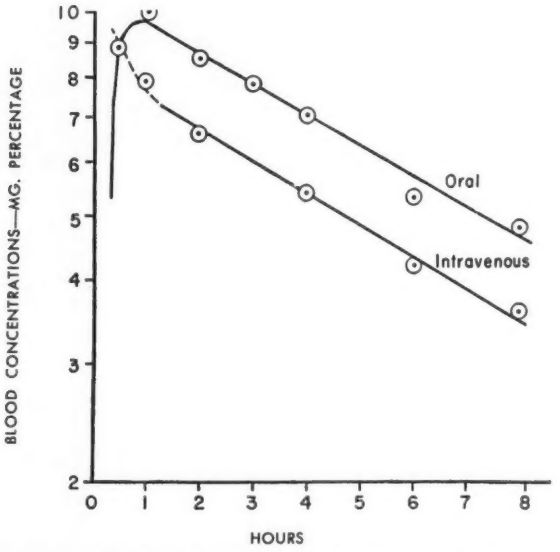


Figure 2. Free sulfaethidole concentrations in the blood for a single human subject following two-gram oral and intravenous doses.

drugs. Both the gastric mucosa and the intestinal mucosa appear to be preferentially permeable to the undissociated form of drugs. The extent to which a weakly acidic or basic drug is in the undissociated form in an aqueous solution is related to the *p*H of the solution and the pKa of the drug. Weakly acidic drugs dissolved in the acidic fluid of the stomach may be largely undissociated and may be absorbed quite well from the stomach.

Upon entering the duodenum, substances are subjected to the digestive and leaching actions of the intestinal fluids, and these actions may be enhanced by intestinal motility. Peristaltic waves, uncoordinated contractions and relaxations of segments of the intestine, and movements of the body aid in the movement and digestion of material in the intestines.

Bile salts from the liver, and proteinases, lipases, and amylases secreted by the pancreas and intestinal glands aid in the dissolution and digestion of materials entering the small intestine. The enzymes of the intestinal tract require a less acidic environment for optimal performance than that present in the stomach, and we know that the *p*H in the small intestine is maintained at from 4 to 7.5, varying along the length of the tract.

Weakly basic substances may be absorbed quite well from the small intestines, though not so well from the stomach. Strongly acidic or basic substances generally are poorly absorbed throughout the tract.

Normally food substances require 10 to 25 hours to pass through the 25 feet of small intestine of an adult human, and an additional 10 to 25 hours to pass through the large intestine. Drugs in the small intestine may be absorbed into the blood via the capillaries or, in the case of some fatty materials, they may enter into the lymphatics en route to wider distribution in the body. Though most orally administered drugs are absorbed from the stomach and small intestine, some drugs are also absorbed from the large intestine.

Design of Sustained-Action Products

In designing a sustained-action product, we must thus keep in mind the attrition to which the product is exposed as a result of digestive fluids and gastrointestinal tract motility; the variable rate of movement through the tract; and the variabilities of the tract environment with regard to *p*H, food, salt, and enzyme content. In light of the variable physiologic and biochemical environment to which a sustained-action product is exposed in the tract, it is apparent that the development of a useful product must be based largely upon the effects water and physical

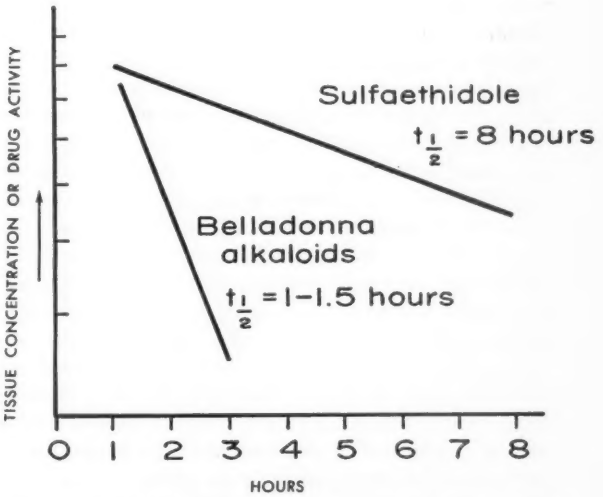


Figure 3. Graph illustrating relative differences following a single dose in disappearance of drug or drug activity from the human body.

attritional forces of the tract have on the product over a period of time. I know that, in the case of our products, the controlled variation of film thickness in the hundreds of pellets constituting each dosage unit results in a regulated permeability by water. In turn, this regulated permeability helps regulate the rate at which the drug moves out of the pellets and

(*Continued on page 548*)

MAKING Sustained-Action Oral Dosage Forms*

BY MANFORD J. ROBINSON SMITH KLINE & FRENCH LABORATORIES

There must be certain standards for both the product and the method used in the preparation of the sustained-action dosage form. We can illustrate some of these criteria by examining data which we have accumulated on sulfaethidole (SETD), a sulfonamide. First, the product should, in most instances, provide as rapid an onset of action as the drug absorption rate will allow. To provide this rapid onset, a quick-release portion of the drug equal to the required initial dose should be available for immediate dissolution. For sulfaethidole we assume that the optimal therapeutic blood concentration is about 10 mg. per cent. An initial dose of approximately 2.0 gm. will provide this blood concentration.[2] After this therapeutic level has been reached, the maintenance portion of the dose should be absorbed at a relatively constant rate—one approximately equivalent to the rate of the drug's disappearance and/or degradation; that is, the rate *in* should equal the rate *out*. If we examine the excretion curve of this drug we see that the elimination rate (k_b) is about 10 per cent per hour. If we then administer hourly doses of approximately 220 mg., we will attain a relatively constant blood level. To attain these levels, the product should[3] release its drug so that a plot of cumulative amount dissolved with time is a straight line. Practically, however, most of the commercially available sustained-action dosage forms show some departure from linearity; that is, the rate of drug release decreases over time. Commercially, it is desirable to limit our dosage form to a single dosage unit, such as a single tablet which contains both quick-release and maintenance portions. The therapeutic level, then, in most instances must be allowed to subside at the later time periods to allow for the surge which will, in most instances, be associated with the quick-release portions of subsequent doses. Where dissolution from the sustained-action portion of the dosage form is nonlinear (and for drugs which are rapidly absorbed and more slowly excreted), the level should be allowed to subside at even earlier time periods. The combination of somewhat nonlinear dissolution and the subsiding of the therapeutic level during the later

hours may result in some nonuniformity of response. However, a minimum criterion would seem to be this: the therapeutic response from the total sustained-action dosage form should be within the limits obtained from the usual multiple daily dosage regimens. More desirable is a response that approximates that obtained from hourly administration of drug. Using the equation, $W_t = W_o + W_o k_b h$, we find that our total dose for a sustained-action form of sulfaethidole is about 3.9 gm.[4] The sustained-action dosage form of sulfaethidole containing this amount of drug provides a therapeutic level that corresponds quite well with that observed for the hourly dosage regimen.

Although in formulating a sustained-action product we are prolonging absorption time, generally there should not be a significant decrease in absorption efficiency. The amount of total drug absorption should be roughly equivalent for both the sustained-action and multiple-dosage regimens. Recovery of sulfaethidole from the sustained-action dosage form given every 12 hours is essentially complete (95 per cent) after 96 hours.[4] This corresponds to the amount recovered when crystalline SETD is administered.[5]

In order to meet the foregoing criteria we should, of course, choose a method for the preparation of our sustained-action dosage form which will allow us selectively to modify our dissolution rate. The method used in preparing the product should be such that manufacturing is sufficiently simple so that it can be prepared by any competent compounder. Simplicity of method will also help to insure good repro-

*Presented at the St. John's University Pharmacy Congress, Jamaica, N. Y., March 1960.

ducibility from lot to lot and dose to dose. The product should be stable over its stated or anticipated shelf life. Finally, the product must be acceptable to the patient and to the physician.

Sustained-action dosage forms generally are marketed as tablets, capsules, or liquids. Selection of the dosage forms for development will depend not only on the ultimate consumer but also on the total dose requirements. Tablets or capsules are generally preferred for most adults; liquid suspensions for pediatric and, in some instances, geriatric use. If the dose is somewhat large, a liquid suspension or a powder for reconstitution before administration may be the indicated dosage form.

Generally, providing for the quick or immediate release portion of a sustained-action dosage form is not a particularly difficult problem compared to that of providing for sustained action. For purposes of this discussion we may divide the methods used for providing sustained action into two broad categories, which, for lack of better terms, we will call chemical and physical. Sustained-action dosage forms prepared by physical methods may conveniently be divided into the broad categories of capsules, tablets, and suspensions.

The first oral sustained-action dosage form was introduced in 1952.[1] It consists of small spherical pellets filled into hard gelatin capsules. Here the pellet nuclei can consist of the drug itself or other materials such as sugar. If a material such as sugar is used, the drug can be coated directly on the pellets by suitable pan-coating techniques. Drug is available from these pellets for immediate absorption. The sustained portion is prepared by the application of multiple coats to drug or drug-coated pellets.

Blythe,[6] discloses the use of fatty alcohols, acids, and esters and, specifically, the combination of glyceryl monostearate and beeswax as coating material. Certainly most coating materials that are stable and control the rate of fluid permeation, and thus dissolution, are satisfactory for this purpose. The desired dissolution rate is obtained by proper selection of the coating materials and by varying the range of thickness of the selected coating. Size of the finished pellets is, generally, in the range of 16 to 25 mesh. Rather close control of the mesh size of the finished as well as the starting pellets facilitates control of capsule-to-capsule variability. Because of the multiple-colored pellets in the capsules, it has been suggested that this type of medication dissolves in distinct surges somewhat similar to repeat-action tablets. As Blythe[1] and others have shown, this does not occur. The "controlled random thickness" of coating on hundreds of pellets actually provides a rather smooth and constant dissolution over the desired time period.

An alternative to this procedure is to granulate medicament in a conventional manner, using suitable fillers. If the granules are somewhat impermeable or preferentially permeable to the gastrointestinal fluids, a type of prolonged dissolution will occur.

The sustained action obtained by the granulation method is a function of surface area as well as the matrix used. Generally, the amount of drug released with time will be nonlinear, as previously discussed. The initial amount of drug released may also be too great for many drugs, unless the granules are further coated as is done with pellets. Materials suggested to prolong dissolution include agents such as ethyl cellulose, metallic soaps such as aluminum stearate, various polymers such as the methacrylates, polyethylene, etc., and agents such as fatty alcohols and esters.[7-9] Some difficulty may be encountered in controlling the mesh size and exposed surface area, which are obtained by normal grinding techniques. Rosenthal[10] suggests the use of zein to retard dissolution, and an extrusion process to form granules, which may result in a more uniformly shaped granule. A Rohm and Haas patent[11] also discusses the use of fusion, polymerization, and molding, as well as extrusion, to prepare the imbedded drug pellets.

Svedres[12] discloses a method of compressing granules into tablet form. He uses dried sugar solids as the conveying matrix. The medicament leeches slowly from the tablet as it disintegrates, and the rather large amount of drug found in the surface is used to provide both the initial and the sustained action of the medicament.

We can also provide a type of sustained action by simply compressing a tablet with a minimum or no disintegrant so that it will dissolve very slowly over time. The quick-release portion can be pan-coated over the slowly disintegrating core, or added by compression using a two-layer press or a press-coating machine. If necessary, the drug can be dispersed in or granulated with a suitable matrix further to delay its dissolution, as suggested by Svedres. Swintosky[13] recommends the use of a multiple-layer press; Cooper,[14, 16] a press-coating procedure; and Hermelin[15] a multiple-granulation procedure using shellac as the dissolution retardant. In addition to shellac, these inventors also suggest the use of fatty alcohols, fatty acids, esters, etc. Swintosky[13] states that a more uniform dissolution will be obtained if relatively thin flat-faced tablets are made. Stempel[17] states that one manufacturer employs the technique of coating the medicament over a slowly disintegrating core that also contains the medicament. An interesting modification of this technique has recently been mar-

(*Continued on page 555*)

HAIR BLEACHES

BY MARVIN K. COOK CONSULTING CHEMIST

COURTESY CLAIROL INC.

Hydrogen peroxide, used as a hair bleach for nearly a century, is still considered the most effective agent for this purpose. Practically all commercial peroxide bleaches and dye developers consist of 20 volume (6 per cent) solutions. The designation of hydrogen peroxide as 20 volume indicates that one volume of solution will yield 20 volumes of oxygen. This terminology is rather antiquated; concentration is most accurately expressed as percentage by weight.

In bleaching, there is often the possibility of damaging the hair. The ideal situation would be to oxidize only the natural hair pigments but, unfortunately, the proteins of the hair are simultaneously affected —adversely. The cysteine-disulfide linkages that bind the polypeptide chains of keratin are essential to hair structure; these apparently become ruptured during the bleaching operation with resulting weakening and loss of elasticity of the hair. Overbleaching will eventually cause embrittlement, as will the cumulative effects of repeated treatments.

It was found that, after oxidizing the hair with hydrogen peroxide, a colloidal substance is relinquished when the hair is washed, as evidenced by the presence of a cloudy material in the warm wash water. The substance is believed to consist of the water-soluble oxidation products of keratin. Since acidic substances having a *p*H below 3.8 precipitate this soluble, proteinaceous matter, it was assumed that an acid rinse, directly following bleaching, would insolubilize the water-soluble substances and keep them in the hair shaft where they belong.

Shampooing or even rinsing the hair after bleaching could be quite detrimental, according to these recent findings. By utilizing a suitable acid rinse after the completion of the bleaching process, the hair is favorably strengthened. Organic acids, such as tartaric, may be used in formulating acid rinses.

A proposed method of estimating hair damage from bleaching consists of testing the hair with Orange II. Solutions of this acid dye will be absorbed by normal hair and will fade. Bleaching will reduce dye uptake, seemingly in direct relationship to the degree of oxidation. Strongly bleached hair will not absorb any of the dye. Interestingly, acid rinsed, bleached hair will behave like normal hair when treated with Orange II, unless it has been severely damaged.

Despite these drawbacks, the alkaline-peroxide mixture when suitably modified offers at present the best, and probably the safest, means of bleaching. The ammonia not only induces the decomposition of the peroxide to yield active oxygen but serves also to soften and swell the hair, a necessary prelude to bleaching and dyeing. Moreover, ammonia leaves no residue, and the end-product of the peroxide, after utilization of the oxygen, is water.

The simplest bleaching procedure consists of making the peroxide alkaline by adding, for example, approximately 15 drops of 28 per cent ammonium hydroxide to an ounce of 6 per cent peroxide. The hair

COURTESY HELENA RUBINSTEIN

is usually shampooed and, after drying, is treated with the alkaline peroxide solution. The action may be stopped at any stage by washing the bleach from the hair with water.

A number of fundamental bleaching operations are routinely performed in the beauty shop. The use of an alkaline-peroxide bleach on brown hair will yield golden blonde shades. Under the same conditions, dark hair is partially bleached to obtain lighter shades. For producing the platinum shades, in conjunction with toners, total bleaching is resorted to.

Furthermore, a mild bleach may be used merely for lightening blonde hair and occasionally as a softener, to assist the penetration of coarse or resistant hair prior to the application of an oxidation dye. At this point, it is important to mention that the newer oxidation dye-bleach preparations cannot change a very dark shade to a very light shade in a single application. It is at present impossible to change from a dark brown to an ash or platinum blonde, without pre-bleaching.

COURTESY HELENA RUBINSTEIN

By immersing a sample of natural black hair in an alkaline-peroxide bleach, a series of interesting color transformations may be observed. The black partially decolorizes to brown, red, and golden red. Soon after, the red disappears and is replaced by a golden blonde shade. The next shade produced is a distinct yellow and, if immersion is continued, the final color is practically white.

The natural hair colors are conventionally divided into two main groups, consisting of the warm and the drab shades. The warm shades include the reds and golds such as auburn and golden blonde. The drab shades embrace the blacks, neutral browns, ash browns and ash blondes, all of which are characterized by the absence of red tones. Intensity of all these shades is described as light, medium, or dark, with an occasional reference to the intensely dark shades as "jet."

The drab tones usually include jet black, black, jet brown, dark brown, light ash brown, dark ash blonde, medium ash blonde, blonde, and light blonde.

The warm tones comprise dark warm brown, medium warm brown, light warm brown, dark auburn, light auburn, golden brown, reddish blonde, and golden blonde.

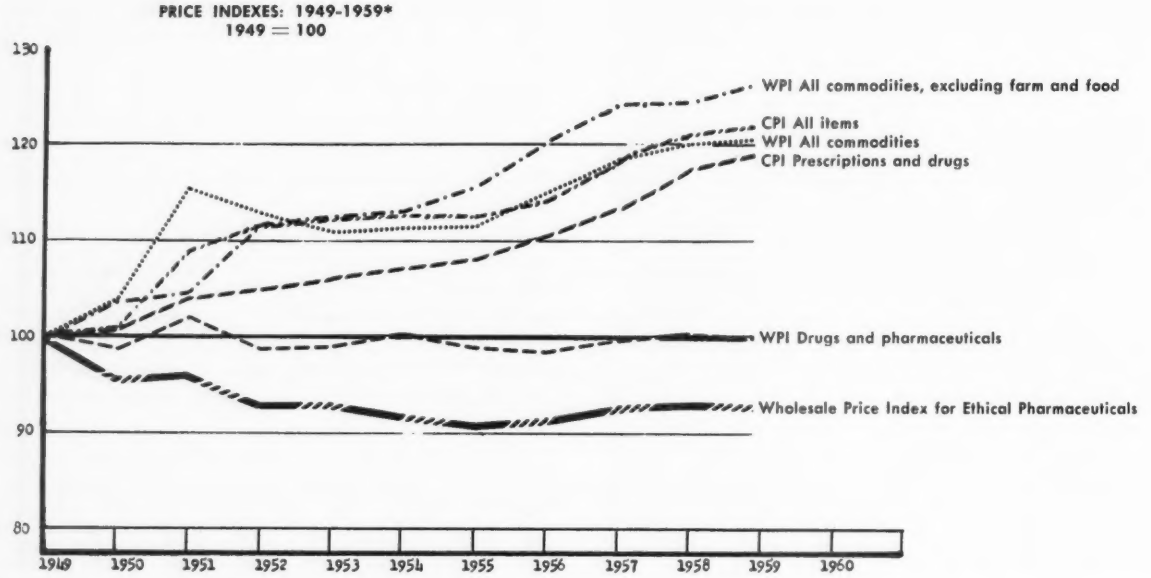
With natural hair, the drab shades tend to bleach more easily than the warm shades. Ash brown and ash blonde bleach readily to golden blonde; black and dark brown change to auburn. Of all the natural hair colors, auburn is believed most resistant to bleaching.

The preparation of stable, dilute solutions of hydrogen peroxide is relatively simple, if essential requirements in manufacture are scrupulously observed. The importance of using proper strength peroxide in bleaching and in permanent hair dyeing must never be minimized. While properly manufactured peroxide solutions will exhibit remarkably good stability, this does not imply indefinite shelf life, particularly under varying conditions of temperature and storage.

Hydrogen peroxide is available in a number of grades and strengths, the 35 per cent solution by weight is probably the one most often used for preparing dilute solutions. Since the concentrated solutions may irritate, avoidance of contact with the skin, eyes, and mucous membranes is advised. In the event that contact is made, prompt flushing with water is suggested as the best countermeasure.

The purity of the water used for dilution is of considerable importance; only deionized or redistilled water is recommended. A major peroxide supplier

(Continued on page 558)



*The Wholesale Price Indexes and Consumer Price Indexes are prepared by the United States Bureau of Labor Statistics.

A PRICE INDEX FOR DRUGS*

BY JOHN M. FIRESTONE, Ph.D., PROFESSOR OF ECONOMICS, THE CITY COLLEGE OF NEW YORK

Prices and costs of drugs have suddenly been spotlighted by the Kefauver Sub-Committe on Antitrust and Monopoly and brought to the attention of the American public. Particularly dramatic was the assertion by the Committee's economist, Dr. John M. Blair, that the manufacturers' markups on drug specialties to the pharmacist were as high as 1,118 per cent, and to the public 7,079 per cent. These charges produced headline stories across the nation. However, within a day following this sensational disclosure, many newspaper editors across the land, after sober reflection, denounced these assertions as misleading.

Let us look into the course of wholesale prices for ethical prescription pharmaceuticals over the past decade; it is first necessary, however, to clarify the distinctions between the costs of drugs and the prices of drugs. These two concepts are too often confused —changes in drug costs are thought of as changes in drug prices. The principal distinctions that should be made for the consumer are these:

1. If we increase or decrease the quantity of drugs we use, our drug costs rise or decline correspondingly. But this is not a price change.

2. If more expensive or less expensive drugs are substituted for what had been previously prescribed by doctors, total costs for individual drugs change, but not prices.

3. If a new drug is more efficient than its predecessor in the sense that it effects a cure in a shorter period of time and with fewer doses, this means a change in costs, not prices.

4. The introduction of new drugs, such as tranquilizers and the Salk vaccine, where none previously existed, increases the cost of drugs, but this is not a price increase.

5. The drug costs in treating an ailment may have increased, because of the use of new and more costly drugs, but the total cost of the illness including medical and hospital bills may be lower.

6. A discussion of drug costs can present a fair picture of costs only if account is taken of the savings resulting from shorter periods of incapacitation, shorter hospital stays, alleviation of pain, avoidance of costly and dangerous surgery, to say nothing of lives that have been saved.

There is little information on the subject of illnesses or changes in their cost. Studies of this subject, except in isolated instances, present imponderables involving such things as the age of the patient, his vigor, the severity of the illness, and other factors, which too often make direct comparisons difficult and produce results of doubtful validity.

Some indication of the advances in drug therapy may be found in a study by Lucy M. Kramer of the Public Health Service in her article, *Drugs and Medicines* (Public Health Reports, October 1958).

*Adapted from a paper presented at the annual convention of the American Pharmaceutical Association, August 1960, in Washington, D. C.

She reports that 20 years ago a case of lobar pneumonia meant five weeks in a hospital, long convalescence. and 300 to 400 dollars for doctors, nurses, medicine, oxygen, and hospital care. Today it means two weeks of illness, generally at home, back to work immediately thereafter, and 15 to 30 dollars for drugs. Thirty years ago the treatment of mastoiditis cost at least $1,000, required surgery, and involved the possibility of permanent impairment of hearing and loss of life. Today $15 worth of antibiotics clears up most cases without surgery. Thirty-five years ago, the son of President Coolidge died of septicemia, despite the best of medical care. Had sulfa drugs been available, this life would have been saved, and he probably wouldn't have spent a single day in bed in the process of recovery. Today syphilis is often cured or at least brought under control with one shot of long-acting penicillin. In the United States, penicillin has completely supplanted other forms of drug therapy such as arsenic and bismuth. New drugs have helped reduce deaths from tuberculosis. Between 1946 and 1955, a mere ten years, the tuberculosis death rate dropped from 34.9 per 100,000 to 9.1 per 100,000, a decrease of almost 75 per cent. Many patients are now cured at home in a small fraction of the time and cost it took when prolonged rest in a sanatorium was the major technique. The recent discoveries of drugs for the treatment of mental illness have made possible the return from mental hospitals of thousands of patients to their homes and communities.

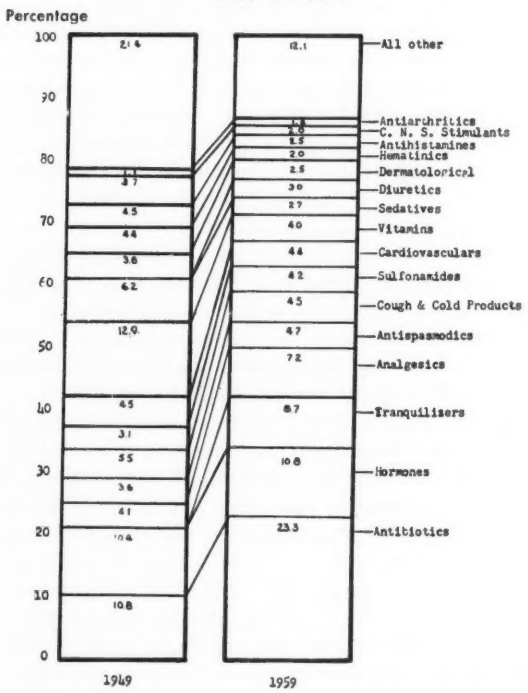
On the other hand, the treatment of many illnesses in the home instead of in the hospital makes the families of these patients more keenly aware of drug expenditures. Many of these people had been state wards in mental hospitals and tubercular sanitoriums where their costs had been borne by the state.

This is but a small fraction of the savings that new drugs have produced in restoring health, in speeding recovery, and in saving lives. But none of these studies tell us what has happened to the price of drugs. For this purpose we have used the well-developed technique of price indexes, a simple device for the measurement of composite price movements with respect to both their magnitude and direction of change. It is literally impossible to do this by merely examining the price movements of a myriad of individual items of varying degrees of importance. An index number is a tool for combining these diverse elements into a single composite number, which, when properly constructed, gives a reasonably accurate picture of price behavior.

We have all, at one time or another, remarked that "prices are going up" and much more rarely in these times that "prices are going down." When we do this, we are not thinking of individual items but of the average price behavior. Measuring price changes precisely, and combining these changes in such a way as to measure their true relative importance is to construct an index number. The need for taking account of the importance of the individual items can readily be seen from the fact that a change in the

(Continued on page 562)

RELATIVE IMPORTANCE OF THERAPEUTIC GROUPS
Index of Wholesale Prices of Ethical Pharmaceuticals
1949 and 1959



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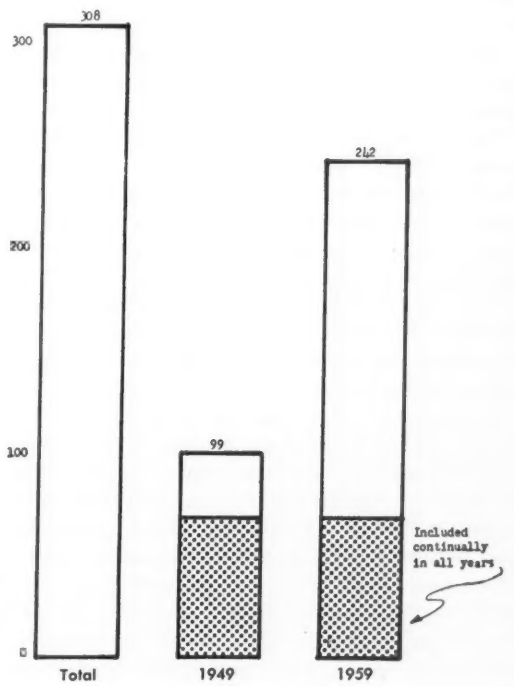


ANTI-STAPH SYNTHETIC PENICILLIN

BY JOSEPH KALISH, Ph.D.

The newest synthetic penicillin has reached the stage of clinical investigation and promises to be an outstanding weapon in the battle a against infections caused by penicillin-resistant staphylococci. First coded as BRL 1241 by Beecham Research Laboratories and as X-1497 by Bristol Laboratories, the compound is 2,6-dimethoxyphenylpenicillin. It was synthesized by Dr. F. P. Doyle in England and is trade-named Staphcillin by Bristol, Celbenin by Beecham. The new antibiotic was announced and described in seven papers in the September 3, 1960 issue of *The British Medical Journal*, and at a conference on "A New Synthetic Penicillin—Experience in the Therapy of *Resistant* Staphylococcal Disease," sponsored by the State University of the New York College of Medicine in Syracuse, on September 7.

In brief, the new penicillin derivative differs from penicillin G in that it destroys staphylococci that are unaffected by the older drug, it is not active when given by mouth, and larger doses are needed for injection. It is similar in that it is remarkably free from toxicity and side reactions and has a closely parallel anti-bacterial spectrum.

The problem of controlling penicillin-resistant infections started almost as soon as penicillin became widely used. New infections began to crop up in hospitals. According to a recent study of the United States Veterans Administration, "The frequency of significant staphylococcal infections in general medical and surgical hospitals ranged between 10 and 13 per cent." These infections, not controlled by penicillin and difficult to cure by other means, are no longer limited to hospitals.

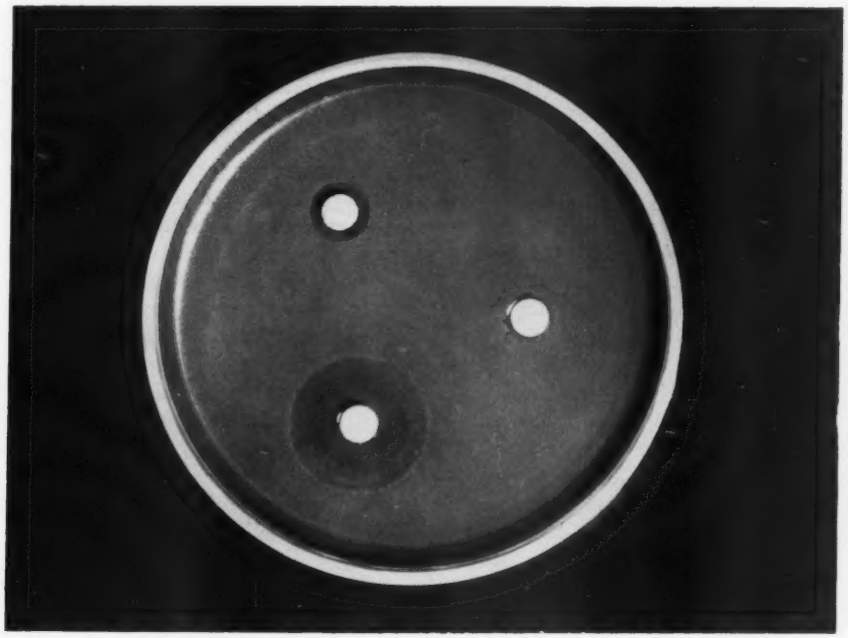
In a statement last year, Dr. Ernst B. Chain, who shared the Nobel prize for the discovery and isolation of penicillin, declared that certain strains of staphylococci produce penicillinase which, destroys penicillin before it can attack the bacteria. These special strains have always been present; they took over when sensitive micro-organisms were checked by penicillin. Therefore, a new penicillin was needed that was antibacterial but unaffected by penicillinase. This is the case with the new dimethoxyphenylpenicillin. According to H. G. Lazell, chairman of the Beecham Group, "The next objective is to achieve the biosynthesis of a new penicillin effective against resistant staphylococci when administered orally."

Summarizing papers presented in Syracuse, the conference chairman, Dr. Paul A. Bunn, noted that the synthetic antibiotic had been administered to 206 patients, of whom 106 had staphylococcal infections, 100 cases being classified as serious. Favorable response was recorded in 79 per cent, a very good record, since 50 per cent mortality might have been expected in these cases. Present indications are that this may well be the "drug of choice" in resistant staphylococcal infections, but more clinical experience must become available before a definitive judgment is possible.

Dimethoxyphenylpenicillin is a pale cream-colored powder that absorbs moisture from the air. It is extremely soluble in water (being administered as a 50 per cent solution), and does not precipitate on boiling. The solution is neutral and the solubility of the penicillin becomes less as the *p*H is reduced, especially below *p*H 4. At neutrality, 30 per cent of potency is lost in 10 minutes at 80° C., and 75 per cent at 100°. As with penicillin G, solutions are slowly inactivated at 37°, at room temperatures, and at low *p*H values.

Either because of inactivation or poor absorption, the drug gives no blood levels after oral administration. After intravenous or intramuscular injection, peak blood levels are reached in one hour; useful levels are maintained for about six hours. About 40 per cent of the dosage is eliminated by the kidneys in about 24 hours, 32 per cent in the first three hours. Oral administration of probenicide, which retards penicillin excretion by the kidneys, permits higher and more prolonged blood levels after injection of Staphcillin. The drug does not accumulate in the body.

Animal tests, confirmed in clinical studies, show the antibiotic to be extremely safe, as is penicillin G, in terms of toxicity and side reactions. Its high minimum lethal dose characterizes very low, acute toxic-



Petri dish showing the power of Staphcillin, the new synthetic penicillin from Bristol Laboratories, to kill "golden staph" germs. Large dark circle around plain white disc shows drug's action on colony of penicillin resistant staph. White disc with narrow halo contains tetracycline, a potent broad-spectrum antibiotic, and the third disc, showing almost no killing power, contains the most commonly used penicillin G.

ity, and it gives no indication of chronic toxicity. Irritation at the site of injection is the same as or less than with penicillin G, and it sems to cause no cardiovascular or autonomic response.

In antibacterial screening procedures, the synthetic penicillin retarded the growth and killed about the same range of micro-organisms as did Penicillin G, but at higher drug concentrations. The outstanding activity is against those staphylococci strains that produce penicillinase and thus resist the action of standard penicillins. The new drug is not affected by the enzyme and kills "penicillin resistant" staphylococci as if they were sensitive organisms that could not manufacture penicillinase.

Clinical investigation has so far verified *in vitro* and animal indications. The new penicillin does not cause toxic side reactions and is effective aginst acute and chronic penicillin-resistant staphyloccal infections, including pneumonias, osteomyelitis, and endocarditis. An occasional patient will develop a rash or show other signs of sensitization, as with penicillin G. More important disadvantages are the relatively large and frequent doses required, but this again underlines the innate safety of the synthetic antibiotic.

The question of sensitization and the possibility of bacterial resistance to the new antibiotic were exhaustively discussed after the presentation of papers at the Syracuse conference.

Sensitivity, which is not a side reaction, involves an individual response by the patient unrelated to possible toxicity. Its manifestation is often erratic and the individual who reacts on one occasion may not do so at another time. A patient sensitive to penicillin G may or may not be sensitive to Staphcillin; the latter has caused reactions in patients who were and were not sensitive to other penicillins. At this stage it would seem wise to consider penicillin G and Staphcillin to be closely related, if not the same, in sensitization potential.

The final consensus concerning the possibility of the appearance of staphylococci that would be resistant to the new penicillin was that this was unlikely. If resistance is due to the emergence of penicillinase-producing strains, then it is likely that these have always been present. They first accounted for a relatively small percentage of infections, but as more sensitive bacteria were kept in check, resistant ones grew in importance. This was not a mutation, but merely a change in growth rates. Other mechanisms may in time become important but, if the present promise is borne out, resistant staphylococcal infections should become progressively less important.

The first of the papers published in *The British Medical Journal* by *A. H. Douthwaite and J. A. P. Trafford* recorded 13 cases of staphylococcal infection resistant to penicillin G and/or other antibiotics which were treated with BRL 1241. The usual dose was one gram at four-hour intervals, equivalent to 10,000,000 units of penicillin G daily. In every case the infection was eliminated.

According to *R. Knox*, the new penicillin in a con-

centration of around 1-4 mcg./ml., inhibits the growth both of penicillin-sensitive staphylococci and of penicillinase-producing staphylococci capable of growing in high concentrations of other penicillins.

In a concentration of 5 mcg./ml., BRL 1241 is rapidly bactericidal to both penicillin-sensitive and penicillin-resistant staphylococci.

Although it is a powerful inducer of staphylococcal penicillinase, BRL 1241 is itself not appreciably destroyed by it. Its activity against penicillinase-producing staphylococci is relatively unaffected by inoculum size, and its antibacterial action is unaffected by concentrations of penicillinase that completely inactivate high concentrations of other penicillins.

Apart from its unique effect on penicillinase-producing staphylococci, BRL 1241 is active, though not in such high dilutions as penicillin G, against a number of penicillin-sensitive organisms.

Comparison makes it clear that different penicillins show quite large differences in the range of their antibacterial activity. It is therefore no longer possible to treat all penicillins as though they were equivalent.

BRL 1241, a synthetic derivative of 6-aminopenicillanic acid, according to *G. T. Stewart et al.*, has a strong bactericidal action on *Staphylococcus aureus*, streptococci of group A, and other pyogenic cocci in concentrations of 1-5 mcg./ml.

Concentrations of this order are readily attained in the serum when children are given four intramuscular injections at a dose of 100 mg./kg./day. Two-thirds of this dosage is excreted in the urine unchanged within a few hours of injection, while a considerable proportion of the remainder is excreted in the bile.

BRL 1241 is much more resistant to the action of staphylococcal penicillinase, and other forms of penicillinase, than benzylpenicillin. It is as active against penicillinase-forming staphylococci as against penicillin-sensitive staphylococci.

In short-term experiments and clinical trials, staphylococci and streptococci did not acquire significant resistance *in vitro* or *in vivo* to the drug.

Allergic hypersensitivity to benzylpenicillin was accompanied in one patient by comparable hypersensitivity to BRL 1241.

BRL 1241 shows a narrower range of activity and less intrinsic actiivty than natural penicillins against various bacteria. The main place of this synthetic compound at present is therefore in the treatment of staphylococcal infections.

The results of investigations on the absorption and excretion of BRL 1241 by *E. T. Knudsen and G. N. Rolinson* showed that a dosage of 1 g. (2 ml.) of the sodium salt, four- to six-hourly by intramuscular injection, would be satisfactory for future therapeutic trials in adults. The antibiotic was well absorbed and was excreted in the urine in a similar manner to penicillin G. No toxic side-effects were noted and no local reactions were observed at the site of injection. If given slowly by deep intramuscular injection BRL 1241 was no more painful than penicillin G.

BRL 1241 was used by *G. T. Stewart et al.* in treating 17 children with infections due to *Staphylococcus aureus* and 12 children with streptococcal infection.

In 14 children with staphylococcal infection and in ten children with streptococcal infection, clinical improvement occurred together with elimination of the organism from the site of infection, though not always, in the case of *Staph. aureus*, from the nostrils of nasal carriers. In only three cases was there true clinical and bacteriological relapse.

In the therapeutic doses used (100 mg./kg./day in four intramuscular injections) BRL 1241 caused discomfort at the sites of injection. There was no evidence of systemic toxicity.

Results obtained by *R. E. M. Thompson, J. L. Whitby, and J. W. Harding* show that BRL 1241 is effective in the treatment of *Staph. pyogenes* infections in mice. When its activity was compared with other antibiotics it was less active than erythromycin and of comparable activity to chloramphenicol and streptomycin. However, in the case of erythromycin it is worth noting that 50 mg./kg. is a large dose, and a comparatively small increase would be apt to give rise to toxic symptoms in the animals, but the dosage of BRL 1241 could be greatly increased without risk of intoxication. It would appear that it is better to treat infections with a single overwhelming dose of this drug. No experiments have been done in animals using penicillin-sensitive strains of *Staph. pyogenes*, but since Thompson et al. found no strains resistant to BRL 1241 among a wide range examined it seems unlikely that treatment of these would be any less effective.

The total isolations of *Staph. pyogenes* in the Middlesex Hospital in the latter half of 1959 and first quarter of 1960 were tested by *R. E. M. Thompson, J. W. Harding and R. D. Simon* for sensitivity against crystalline penicillin G and the new penicillin compound BRL 1241. Only 18 per cent were sensitive to crystalline penicillin G, whereas all were sensitive to compound BRL 1241.

Reporting at the Syracuse conference, *A. Gourevitch et al.* investigated the microbiological properties of 2,6-dimethoxyphenyl penicillin. This penicillin has unique properties with respect to its ability to inhibit staphylococci resistant to penicillin G. Its spectrum was found to be similar to that of penicillin G. However, higher concentrations were required to inhibit the sensitive organisms.

The new penicillin was found to be extremely stable to both staphylococcal penicillinase and *B. cereus* penicillinase. Its activity against resistant strains of *S. aureus* is thought to be due to this property. Investigations studying the effect of inoculum size using a penicillin G resistant staphylococcus indicated that the minimum inhibitory concentration of penicillin X-1497 was independent of inoculum

(*Continued on page 528*)

Packaging and Selling

Chanel No. 5 Presentation de Luxe,
a one-half ounce, classic crystal bottle of No. 5 perfume, plus
a one and one-quarter dram container for the purse in the well-known black and gold. The purse container can be refilled by using the plastic funnel included in the package.

A winning team

needs a "strong bench". When you buy Duraglas containers or their closures from Owens-Illinois, you acquire the rights to a "strong bench" of technical and merchandising skill.

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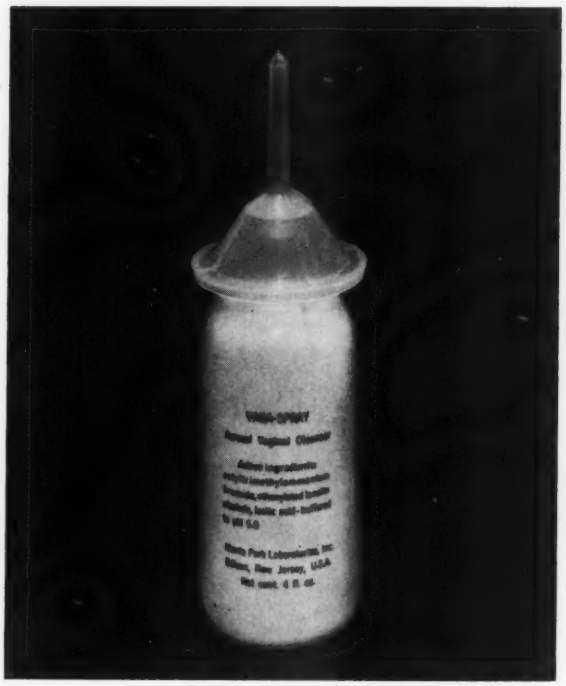


AEROSOL DOUCHE

An aerosol vaginal cleanser, Vaga-Spray, has been introduced as a replacement for the vaginal douche by Menlo Park Laboratories, of Edison, N. J.

The new vaginal spray, believed to be the first developed in the United States, can be used as a cleanser, preoperatively and postoperatively, as preparation for certain medical office procedures, and as a spermicide in conjunction with the diaphragm technique.

Clinical tests and bacteriologic studies were conducted for two year before its introduction, at Perth Amboy General Hospital, Perth Amboy, N. J.

Two surface-acting ingredients with bactericidal, bacteriostatic, detergent, lubricant, and spermicidal properties are combined in the formulation. It is released from a plastic-coated glass bottle as a soft foam through four openings in a short nozzle at the end of a cone. Light pressure on any side of the cone operates the spray mechanism.

The bactericidal action is supplied by cetyltrimethylammonium bromide, which is effective against both gram-positive and gram-negative organisms. It is nontoxic and nonirritating. Vaga-Spray's other principal ingredient, ethoxylated lanolin alcohols, creates a persistent film of the solution on the vaginal mucosa.

The shape of the cone and the shortness of the nozzle permit the ejector to penetrate the vaginal canal only one and five-eights inches, so that introduction into the cervix cannot occur in the normally situated uterus. A nonmetallic aerosol valve, made by The Risdon Manufacturing Company, helps provide the required low-pressure foam. The nonmetallic valve eliminates one potential source of corrosion or contamination in the sanitary package.

The aerosol solution can be applied in two seconds, while the user is lying on a bed, rather than in a tub, as is required with vaginal douches.

The separate plastic ejector can be sterilized in the hospital by autoclaving, boiling, or by cold sterilization, or cleaned in the home by washing or boiling.

Usage of the Vaga-Spray during the two years of testing at Perth Amboy General Hospital, has been under the following conditions, Dr. S. G. Berkow of the hospital reports:

"(1) Preoperative, before vaginal surgery and total hysterectomy, and before such procedures as uterotubal insufflation.

"(2) Postoperative, particularly after cervical cauterization and conization.

"(3) In vaginitis, as an adjuvant (in addition to other local therapy) in trichomonal and monilial vaginitis, and as the sole local therapy in nonspecific and senile vaginitis.

"(4) In conjunction with the diaphragm method of contraception. (An effective spermicide, it replaces both the cream or jelly presently used on the diaphragm and also the postcoital douche.)"

The new procedure is adjudged a safe and effective replacement for the vaginal douche.

Packaging

BERNARDIN closures keep good company!

Borden's new slogan, "Very Big on Flavor," carries a product promise that is indeed very big. To fulfill this flavor pledge, Borden's relies on rigid quality control. For its "Rich Roast" Instant Coffee, this ranges from expert blending of choice coffee beans to selection of container closures which are best fitted for the job of locking in its distinctive flavor. We are proud that Borden's has selected the closure made by Bernardin to ensure full protection of this flavor. *May our Closure Craftsmen work with you?*

SINCE 1881
BERNARDIN BOTTLE CAP CO., INC.
EVANSVILLE, INDIANA

Packaging and Selling

The Vick Chemical Company, 55 years old, is changing its name to Richardson-Merrell, Inc., in October.

The name *Vick* has been intimately identified with the proprietary drug products of this company, but in the last several years its ethical and veterinary drug sales have grown to 43 per cent of total sales.

There was a time, about 20 years ago, when companies trembled at the thought of changing a package. Many of the package changes of that period were planned with minute progressive changes over a series, as many as six packages, in order to ease the consumer from the identification of the old packaging to the identification of the new.

Nowadays, however, nobody hesitates to change a package almost over night, or at least as quickly as the mechanics of change can be arranged, and most people expect an increase of business with a package change. The fact is, nobody seems to be troubled about asking a customer to switch from the identification of one package to another, even when radically different.

However, there is still a great deal of hesitation in changing a company name. The truth must be, however, that if a name has outworn its usefulness, or misrepresents the company's current business or direction, or in any way injures or alters the company's true image, then, the quicker its name is changed, the better.

If you can't lick 'em, join 'em seems to be the new theme song among the big packaging companies. An officer of one of the leaders, in admitting that the second quarter sales were disappointing and competition was terrific among different packaging materials, is reported to have said that he is excited about his company's planned entry into the glass container business.

The company is American Can, which expects to have its first glass plant in production in October, the second one in March of 1961 and, if plans are carried out, six glass manufacturing locations within the next few years. This company is also operating a pilot plant for the manufacture of plastic bottles, but will not begin commercial production this year.

A consideration for entering the already hectic glass business is an advantage the glass containers have over other containers, namely, the cost of raw materials. Raw materials for glass containers, which are pretty inexpensive if the factory is located well, constitute 18 to 20 per cent of the cost of the container; for paper containers, 50 to 60 per cent; and for tin cans, 65 to 70 per cent.

Paper, glass, tin, aluminum, plastic, and what have you, it looks like a boiling, turbulent period ahead for the packaging business.

For some curious reason, the State of California seems to have chosen the perfume industry for a test case on a highly controversial tax issue.

The perfume company selected has a world-renowned name, although its annual sales in the United States do not exceed $2½ million.

The tax controversy concerns an arbitrary decision on the part of the State to impose a gross sales tax on any company doing business in California from a location outside its border. In order to make a test case in this instance, the State's revenue department has seized from a leading department store the accounts payable to this perfume company, which is domesticated in the State of New York.

This issue has come up many times before but, as far as we have read, has been applied only to companies maintaining factories, warehouses, or direct branch offices within a state. This perfume company does not have a factory, or a warehouse, or a shipping point, or a branch office. It operates entirely through a commissioned salesman who covers the entire Pacific Coast.

The company has temporarily stopped shipping to the State of California, which, of course, is no solution; California is one of its important markets.

One cannot help wondering why California has selected the perfume industry, and a very small company, to make a test case of its taxing powers in a field generally considered unconstitutional.

There seems to be considerable consternation and excitement about a labor contract between a retail clerk's union and some Chicago supermarkets.

As we understand it, the stores have agreed with the union not to allow manufacturers' salesmen to arrange their own particular branded products on the stores' shelves. In the future this work will be the exclusive province of the stores' employees.

This, undoubtedly, could be bad news for a lot of major manufacturers in the food field. To many powerful organizations with tremendous numbers of direct salesmen it has been a potent, competitive advantage over many other manufacturers to give a few manufacturers' salesmen such a competitive and

OPAL . . . the aristocrat of glass
For beauty, utility and all-around satisfaction, opal jars are the most desirable containers for cosmetic creams.
Carr-Lowrey brings you opal jars and bottles at their best. Decorated with your own attractive design, they are outstanding containers for your finest products.
complexion
CREAM
GLASS
STIMULATES
SALES
deodorant
CREAM
cleansing
CREAM
CARR-LOWREY
GLASS CO.
Designers and manufacturers of fine glass containers
Factory and Main Office: BALTIMORE 3, MD. • New York Office: 415 MADISON AVE. • Chicago Office: 1572 MERCHANDISE MART

discriminatory advantage in arranging products on the shelves.

Several months ago, this department carried a story about the downright dirty, vicious competition that was taking place in California among the baby food manufacturers, whereby competing salesmen of the two leading brands, who were admitted to grocery stores to arrange their own products on the shelves, were displacing competitors' products, denting the cans, messing up the labels, and a variety of nice, pleasant, little accidents of that sort.

There isn't any doubt that the number of salesmen who have been allowed this privilege in any store have been a fraction of the salesmen calling on that store, and that it has been a drastically unfair, competitive advantage to these few.

We can understand the howls of anguish from manufacturers who may be denied this privilege. At the same time, we think it is a healthy movement in the direction of better distribution if the retailers of this country, who are selling their birthright in so many of the proper functions of retailing, should begin taking over some of these lost functions for themselves. We think it is a darned good idea for retailers to stand on their own feet and do more of the job that properly belongs to them and for which they are liberally paid by the present discount rate of manufacturers, rather than to delegate more and more of their duties and functions to the dominating manufacturers.

The Brand Inventory Survey for 1960 by the *Des Moines Register and Tribune* has just arrived.

This is another of those useful and comprehensive surveys prepared each year by a group of metropolitan newspapers.

Among the information to be found in this survey is the amount of usage, over a period of years, of various products like those listed below.

Percentage of Use by Families	1954	1960
Hair tonic for men	74.9	82.1
Hair tonic for women	49.2	55.7
Home permanents	39.2	31.1
Lipstick	88.0	91.9
Face cream	71.4	81.5
Shaving cream-aerosol	27.4	42.8
Cold remedies	32.7	70.9
Chest rub	72.5	85.9
Headache remedies	89.2	96.1
Nose drops	41.0	52.9

Coty is a newcomer in the field of therapeutic or medicated cosmetics, with Dermacare, a medicated treatment kit from the company's pharmaceutical division. It includes a foam wash, a medicated make-up cream in six shades, and a night lotion.

The introduction of this kit is part of Coty's program to change its image from makers of products "that grandmother used to use" to makers of products for teen-agers and young women.

Some time ago, Coty had an investigation made to discover its company image among consumers, and was somewhat shocked to find that a high percentage of the women questioned said that Coty products were favored by grandmothers.

New advertising will appear in *Good Housekeeping* and *Seventeen*.

Ciba Pharmaceutical Products has given up its open-circuit television for doctors.

Local station tests have shown that, although the general public could tune in on the company's program, the technical language used and the highly professional presentation of the product discouraged public interest. Nevertheless, the American Medical Association has formally objected to it on the basis that it would set a bad precedent and that the public might listen in.

We think the A.M.A.'s stand sets a bad precedent. In effect, the Association is thus forbidding manufacturers the use of a tremendous and primary means of communication.

We also think that this aura of secrecy and the policy of insulating the public from medical information is bad public relations, and, very probably, extremely short-sighted.

One of the leading companies in the men's field has been telling suppliers that a recent survey of theirs shows the men's market for toilet goods to be $300,000,000.

This is something we cannot figure out. If the survey includes razors and razor blades, which we guess it does not, the figure could be correct. But even if this figure is for retail prices, in our opinion, it is far too high.

It would be nice to know just how big this market is, particularly in after shave lotions, men's cologne, and men's deodorants. It is an expanding, dynamic one with a long way to go, but we doubt that its total has passed much beyond $50,000,000.

It should startle no one to hear that salesmen work harder to maintain their volume when business slows up a little. On the other hand, it is very nice to have the suspicion verified that salesmen really can buckle down and hold up their volume by harder work.

Wheels, Inc., an automobile-fleet leasing company in Chicago, has been doing some statistical work. It reports that, when business is slow, salesmen drive further. For example, salesmen had to drive 10 per cent more miles in the first six months of this year, than in that period of 1959 to match their 1959 sales volume.

The average mileage for a salesman between January and June, was 1,991 miles this year, 1,801 last year.

After ten or more years of tremendous growth, advertising is entering a period of effective criticism from many quarters, particularly political.

EXCEPTIONAL PRINTING MAKES THE DIFFERENCE

on RIGID plastic containers

...helps make the sale!

- Printed or decorated up to 4 colors on crystal clear, transparent or opaque colors
- Largest line of RIGID plastic containers
- 1/5 the weight of glass—greatly reducing ever-increasing shipping and handling costs
- Lightweight and shatterproof—with rigid wall protection
- Economical—with customer re-use value
- Also made of new high density polyethylene —Poly-Opal*. Are chemically inert, stain resistant and have lower permeability to moisture and gases than conventional polyethylene.

*T. M.

Write for full-color catalog, samples and prices.

LERMER PLASTICS, INC.

574 SOUTH AVENUE, GARWOOD, NEW JERSEY

PIONEERS AND SPECIALISTS IN PLASTIC CONTAINERS SINCE 1919

It seems to us that anyone who is objective must admit that, during these ten or more years, a great many bad practices have crept into advertising, making it vulnerable to sharp criticism on moral or ethical grounds, on social grounds, and definitely on economic grounds.

A great many advertsing leaders are springing to its defense. Some speak in a restrained, positive way, but others rant in such a way as to call to mind the assailants of the original Food & Drug Act and the original Securities Exchange Commission.

We are, however, happy to print here some extracts from a talk by Howard J. Morgens, president of Procter & Gamble Co. This is a positive presentation of the social and economic importance of advertising to America by a man whose company is one of the top three in the world in advertising expenditures.

"There are certain broad basic reasons for advertising's great effectiveness—reasons which go beyond mere dollars and cents calculations. They are fundamental to any appraisal of advertising from a general management point of view and they comprise my next few points:

"*Advertising can and does create new markets.* It can do this more rapidly, more intensively, and less expensively than any other method of selling the consumer.

"In our own industry the rise of personal cleanliness has closely paralleled the rise in advertising of soaps and detergents in every country in which we do business. In the United States, the social desirability portrayed by advertising of the daily bath, the daily clean shirt, and clean white teeth have produced cleanliness habits which are still relatively new in our society.

"This is not to contend, of course, that advertising *created a desire* for cleanliness where none existed previously. Only small boys have ever contended that it was not desirable. What advertising did was to remind people of something they wanted and to tell them about products that encouraged and facilitated cleanliness.

"This general point about advertising's ability to create new markets does not need much positive documentation here. In fact, advertising is currently being criticized in some quarters for doing this job too well. It is said to force people to buy products that they do not want. I'd like to digress just a moment in an effort to clear up this misunderstanding.

"I'll say categorically that no amount of advertising can force any large number of people to buy things they do not want. Advertising can only create a new market for products which fill a genuine—though often unexpressed or latent—consumer want. In other words, advertising cannot develop a consumer want except where the need or desire previously existed—even though it may have existed in unrecognized or dormant form.

"This is more than just semantics. Some people may say that what people are unaware of, they don't want. In the same sense that 'ignorance is bliss,' that's true. But people certainly won't buy a great many things that they might be made aware of. The basic need or desire must be there to begin with.

"This is also more than just a theory. Let me illustrate how it works in actual practice:

"Before setting out to create a new market for a new type of product, most sophisticated companies go through a process of testing that product with the consumer.

"As part of this testing process, a group of people are asked to use the product 'blind'—that is, without exposure to advertising, without a brand name, without labels or glamorous packaging. If the consumers so tested respond to the product favorably, if they recognize it immediately as 'something they've wanted' or 'would like to have'—then the company involved has a chance to develop a new market for it.

"On the other hand, if—in the testing process—consumers should not respond favorably to this new type of product *when exposed to it without advertising*, then the surest way to go broke is to spend advertising money trying to create a new market for it.

"There may be exceptions to this. However, based on our own experience, it is about 99 44/100 per cent correct!

"Another fundamental point about advertising is that properly used *it does lower costs to the consumer.* This is another point that never seems to be adequately understood.

"It is true that advertising does, in itself, add to the cost of a product. However, it also results in savings that—in most instances—are greater than the cost of the advertising. It does this in many ways.

"A. *It brings about savings in manufacturing costs.* This is well-known, of course. Advertising helps produce large volume on specific standardized items and this is what makes mass production methods possible.

"B. *Advertising also brings about savings in other types of distribution costs.* The high volume which it creates lowers the salesmen's cost per unit. It also means rapid turnover for the retailer, which in turn makes lower retail margins possible—without reducing the dealer's profit on capital invested in inventories or shelf space. In this way advertised brands have helped make the low cost supermarket operation possible. And dealer margins, as I said, are one part of the total cost of distribution.

"C. *Advertising also brings about savings in buying, financing, and in many other business operations.* Properly used, it tends to produce more stable volume week in and week out. Stability of volume results in great efficiencies and economies in practically everything that a company does. Time and again in our own country, we have seen the start of

advertising on a new type of product result in savings that are considerably greater than the entire advertising cost. When we consider all types of production costs, all types of distribution costs, and all other operating costs, the use of advertising clearly results in lower prices to the public.

"Once a mass market has been created for a certain type of product—and once mass production equipment and techniques have been developed for that type of product—it is, of course, possible for someone else to take a free ride for a time by selling the same type of product at a lower cost by not using advertising. However, it would be a great fallacy to go on from there and to infer that all such products would be cheaper if there were no advertising on any of them. In fact, the contrary would be true.

"Probably the most important point about advertising today, and one that is least understood, is *its role in product improvement*. It plays a tremendous part in the constant upgrading of consumer products.

"Advertising cannot sell a poor product. It might induce people to try it once. But it cannot build an enduring business on such a product. That has been proven over and over and over again. In fact, the quickest way to kill a brand that is off in quality is to promote it aggressively. People find out about its poor quality just that much more quickly.

"I'll go further. Advertising cannot sell a product for very long in a competitive market if that product stands still quality-wise!

"Advertising offers a quick effective way for anyone to tell the world that he has improved his product. Assuming the improvement is genuine, the public is quick to notice it and the return on the advertising expenditure is greatly enhanced. There is a constant struggle, as you know, to make one's marketing dollars work more and more effectively. This struggle acts inevitably as a spur to the development of better and better products.

"Research people, of course, are constantly searching for ways to improve the things we buy. But believe me, a great deal of the prodding and pushing and suggestions for those improvements also comes from the advertising end of the business. That's bound to be because the success of a company's advertising is closely tied up with the success of its product development activities.

"Furthermore, when a company is confident of its ability to acquaint the public quickly with a product advance, it is more willing to invest dollars in the research which is needed to bring that improvement from the labortaory to the consumer.

"In this way, advertising and scientific research have come to work hand-in-glove on a vast and amazingly productive scale. No other form of consumer selling has yet demonstrated this ability to foster product innovation. The direct beneficiary is the consumer, who enjoys an ever-widening selection of better products and services.

"All of these points bring me logically to still another one which is so obvious to us who know advertising that it often goes unexpressed.

"It is that *advertising increases competition.*

"Many of us here can remember in the 1930's and early 1940's when advertising was frequently criticized in academic and governmental circles for being wasteful, ineffective, and parasitical. One of the purposes for starting the Advertising Council was to demonstrate the effectiveness of advertising to people in government by using it in public service causes.

"Today, the pendulum has swung to the other extreme. Advertising is now being criticized for being too effective. It is so effective, we are told, that it may lead to monopoly and restraint of competition.

"This criticism is most certainly based on a misunderstanding because one of the most fundamental characteristics of advertising is that it *forces* one to be competitive."

Schiaparelli is tying up with 20 Mule Team Borax in a big national promotion. The Schiaparelli product will be a new aerosol product retailing at $5, but given for $2 plus a Borax box top. There will be 3,480 TV spots used in 130 markets during a 6-week period, plus other spots on "Death Valley Days," sponsored in 75 markets by the 20 Mule Team products department of U. S. Borax & Chemical Corp.

In this promotion 20 Mule Team will depart from its normal black-red-white colors and will adopt the "Shocking Pink" color.

In order to overcome the expected resistence of department stores and the prestige stores which carry Schiaparelli, this premium will be in a new package that is the first metered aerosol spray in this line. In other stores the spray atomizer will be used. Also, the Mary Chess detail men are expected to get trade approval by pointing out the heavy TV advertising and in-store promotion given to this product.

In addition, a "bonus dollar" coupon is enclosed in each premium package. This coupon is good for $1 toward the purchase of any one of three Schiaparelli products in other stores.

Ar-Ex Products Company, a Chicago cosmetic firm, is celebrating its 25th anniversary as a manufacturer of hypo-allergenic cosmetics.

This ethical prescription cosmetic company, which was founded on a $700-shoestring by Julius B. Kahn in 1935, has now grown into a substantial cosmetic company doing an annual business of over $1 million and making more than 135 hypo-allergenic products.

This aspect of the cosmetic industry rarely intrudes on the general publicity scene. However, it is by no means an insignificant part because statistically 15.5 per cent of all women using cosmetics, or nearly 7 million women, are allergic to some form of cosmetics. It is said also that a high percentage of these women are not aware of the cause of their allergic troubles.

News in Packaging . . .

Featherweight Plastic Shipping Containers

Allied Chemical's General Chemical Division has developed a lightweight plastic shipping container for use with its Baker & Adamson laboratory chemical line. Weighing little more than a pound, the expanded polystyrene case has passed the ICC drop-test requirement; ICC tests require that such a case withstand a single drop from a height of four feet, without damage to the bottles; General's case withstands 16 separate drops from that height, without damage to the bottles.

The lightness, strength, and shock and weather resistance of the case derives from low-density expanded polystyrene. Its safety and ease in handling for reagent acids is outstanding, and the formed pockets are a marked departure from the straight-walled bottle cells of conventional shipping cases.

The case is also smaller than conventional cases, measuring 13½ inches in length and width, and 14 inches in height. Tare weight with empty bottles is less than 11 pounds, which saves freight costs.

An interlocking design for safe stacking appears on top and bottom of each case. Convenient finger grips ease lifting and carrying. A single strip of pressure-sensitive paper tape binds the upper and lower halves of the case, which fit together as do the sections of a suitcase, but without hinges. This strip, as well as the label, is color-coded to denote the contents, either yellow, blue, red, or green.

Suppliers of the components are Koppers Company, Inc., Dylite-expanded polystyrene; Owens-Illinois Glass Company, glass bottles; Armstrong Cork Company, Inc., bottle caps; and Behr-Manning Company, pressure-sensitive tape.

Metered Oral Dosage Valve

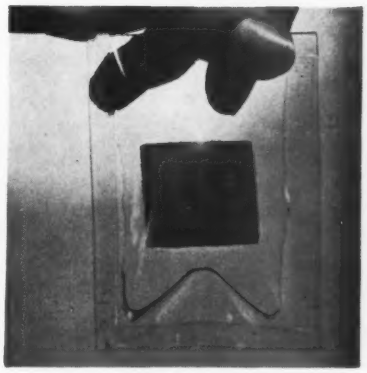
A metered attachment for accurate control of oral doses either as spray or aerosol is now available from Emson Research, Inc.

The Emson Oral Attachment, made of Super Dylan plastic, is designed for simple, instantaneous operation to aleviate sudden asthmatic attacks. Slight pressure on the activating button releases a metered amount of medication.

Constructed for maximum protection, the unit is compact, easy to carry, leakproof, dustproof, and virtually foolproof in operation. It fits on standard 20 mm. valves, which are generally used with glass bottles, and also special stainless steel containers patented and produced by Emson.

To use the attachment (see photograph below), the top is removed and placed horizontally on the valve button. Pressure on the button activates the valve, directing medication into mouth and lungs.

Emson manufactures the metered valve, steel container, and oral attachment. The package, complete with attachment, may also be used for virtually any oral medicinal throat spray, mouth wash, or breath freshener.



Handipak, produced by a machine manufactured by Packaging Services, Inc., which inserts a small article and fills a precise amount of liquid in a leakproof, flexible film package.

Polystyrene Cosmetic Jar

Celluplastic Corporation has developed a heavy-wall cosmetic jar of polystyrene with closures of the same material. For more positive sealing, closures have a pulp and vinyl liner.

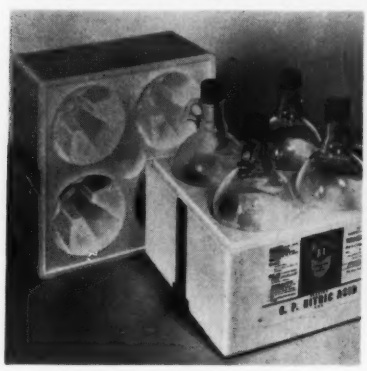
Available in capacities of 1, 2, and 4 ounces, the jars are tapered slightly from top to bottom. They are stocked in opaque white, but any standard color can be supplied in quantities of 5000 or more. The jars can be multi-color printed.

Cosmetics Pace Rise in Collapsible Metal Tube Usage

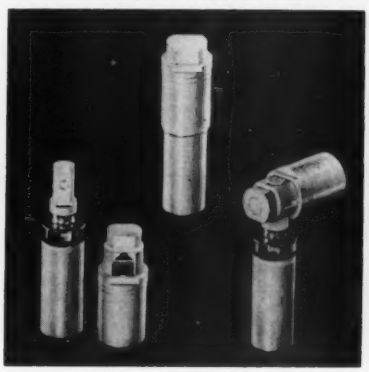
With nearly 60 million collapsible metal tube units sold for skin creams, mascara, and other beauty aids, cosmetics increased its usage in the first half of 1960 by 5 per cent over the same period in 1959. Shipments through June 30th of this year totaled 59,247,648 tubes.

Pharmaceutical tube shipments rose 3 per cent for the same period, totaling 127,491,552; toothpaste shipments rose 2 per cent.

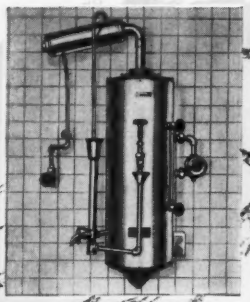
Featherweight, expanded polystyrene case by Allied Chemical's General Chemical Division, cradles four bottles of acid for safe, easy handling. Exceeds ICC drop test requirements.



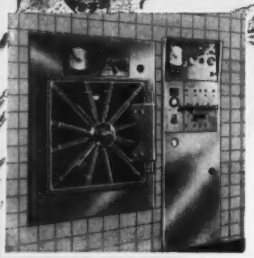
Metered attachment for oral spray dosage, shown at right in dispensing position, developed by Emson Research, Inc., and available for wide variety of drugs, pharmaceuticals.



Design closure for glass aerosol containers by The Walter Frank Organization. The plastic cap of polystyrene has a reverse flare with slightly concave top, clear or in color.



WATER STILLS
Capacities from ½ to 500 gal./hr.
Steam, Electric or Gas Heat.



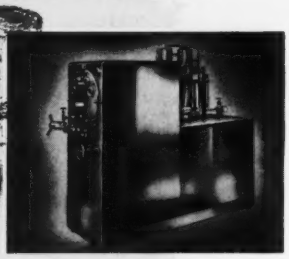
STERILIZERS
Pressure Steam, Gas-Steam,
and Gas. Chambers 16″ x 16″ x 24″
to 60″ x 66″ x 120″.

TALK MICROBIOLOGICAL EQUIPMENT···

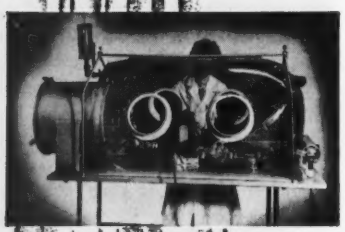
and you have to talk to American Sterilizer!

● Here at Amsco, sterilization is still of prime concern. However, to parallel the great strides of modern biological technology, we've developed a number of highly specialized microbiological devices—all designed to do their job better with less personnel time and attention and at a cost well within practical limits.

If you've a problem in this area, a letter to our Scientific and Industrial Department may lead to its economical resolution.



BIOGEN • *continuous culture apparatus*
For batch or continuous culture of pure microorganisms in controlled conditions.



DRY BOX
Flexible film chamber.
Efficient, economical,
easy to work with.

FREEZE DRY APPARATUS
Laboratory, pilot plant and production models. Used for the preservation and concentration of labile substances.

GERM FREE LIFE APPARATUS
Complete service, including flexible operating, rearing and transfer chamber.

SCIENTIFIC AND INDUSTRIAL DEPARTMENT

AMERICAN STERILIZER
ERIE • PENNSYLVANIA

World's largest designer and manufacturer of Sterilizers, Operating Tables, Lights and related biological equipment

NEWS and VIEWS

BY TED KLEIN PUBLIC RELATIONS DIRECTOR

Where Do You Live?

It may be difficult to determine why, but, depending on where you live, the chances of your dying from coronary heart disease can vary. For example, if you live in Savannah, Georgia, your chances are twice as high of getting a coronary than if your home were in Lincoln, Nebraska.

This information is contained in a study recently released by the U. S. Public Health Service and published in *Public Health Reports*, in August. According to the study, here are the ten cities that had the highest rate per 100,000 white males between 45 and 64 years old.

Savannah, Ga.	826.8
Charleston, S. C.	825.6
Galveston, Tex.	802.1
Norfolk-Portsmouth, Va.	753.7
New Orleans, La.	747.4
Sacramento, Calif.	730.6
Albany, Schenectady, Troy, N. Y.	725.5
Baton Rouge, La.	720.6
Montgomery, Ala.	707.3
Richmond, Va.	706.5

Dr. A. E. Rikli, a co-author of the paper and chief of the Heart Disease Control Program, commented: "Coronary heart disease is one of the most serious health problems in the United States, particularly among middle-age white males. The value of this study is that it pinpoints, for the first time, the specific metropolitan areas where the death rates are extremely high and relatively low. These areas can be thought of as 'natural laboratories.' Investigators in these areas have an opportunity to test out possible environmental factors—such as differences in climate, geological strata, water supply, diet, occupational patterns, and others—to see whether they differ significantly in the high and low areas. Studies to determine the reasons for the great differences in rates are urgently needed."

Generic Drugs

"When a physician prescribes a generic or chemical name product, for your [the pharmacist] own protection, you should insist that the physician stipulate a manufacturer or distributor." So writes Nicholas Gesoalde, executive secretary of the Pharmaceutical Society of the State of New York, in a recent editorial.

He also advises pharmacists that they get the names of manufacturers or distributors of generic products from local welfare departments so that "the liability will fall upon the Welfare Department itself."

This seems well-taken and to the point. After all, it is the physician's responsibility to see that his patient gets the drug he actually prescribes; and, according to Mr. Gesoalde, "When a pharmacist fills a prescription for a generic or chemical drug, he assumes the responsibility of selecting the manufacturer or distributor of that drug. As such, he is fully liable, criminally and civilly, for any adverse effects resulting from the use of the generic product dispensed."

Lilly Song

Under the Eli Lilly signature and a picture of a pharmacist before a music stand with his baton, some common sense advertising has been appearing in July pharmacy trade journals which goes a long way towards encouraging the pharmacist to order from his wholesaler. Under the headline "WORDS (WITH MUSIC) ABOUT THE PHARMACIST WHO CONCERTIZED," the copy gives this message:

" 'Running my pharmacy,' he thought, 'is like conducting an orchestra. I give the old downbeat and in marches the merchandise. Every item at a price . . . like drums beating.

" 'I pay for it . . . with a song.

" 'I sell at a big profit . . . that's a beautiful melody by the entire ensemble.'

"He waved a baton—but nothing much happened that you could call music. And suddenly he realized he was completely off key.

"Moral—A pharmacist doesn't direct the 'orchestra'; he's part of it. The law of supply and demand does the directing.

"The Lilly policy of wholesale distribution recognizes that pharmacists are professional men and not one-man bands. It enables you, the pharmacist, to devote your talents to the practice of pharmacy—leaving warehousing, elaborate bookkeeping, and large inventories to the wholesaler.

"There are more than 300 Lilly service wholesalers to serve you. Just a phone call brings a steady supply of fast-moving, profit-assured items."

Thirteen Million Dollars

The critics of the pharmaceutical industry are quick to push for drastic revisions in the methods used by free enterprise to discover, then sell drugs. I have yet to see one of them recognize the fact that American Cyanamid's Lederle Laboratories spent 13 million dollars on their oral polio vaccine and will not be able to market their product in this country. Here is a perfect example of how our industry works.

Over a period of years, Lederle has given away eight million doses of their vaccine to countries where the cost of any vaccine would have been prohibitive. Millions of children in these underdeveloped nations are now protected because of Lederle's generosity. And, now, when another vaccine has received government approval, Lederle is not complaining about this decision. Instead they are getting ready to make the Sabin Type I strain. In their news release describing their plan, Lederle said:

"We will do our utmost to make our facilities and experience at Lederle immediately available so that the public may have the benefit of an oral polio vaccine at the earliest possible time. However, as is the case with all other biological and chemotherapeutic products, intensive work will continue in our laboratories to make improvements in the vaccine until polio ceases to be a health problem anywhere in the world."

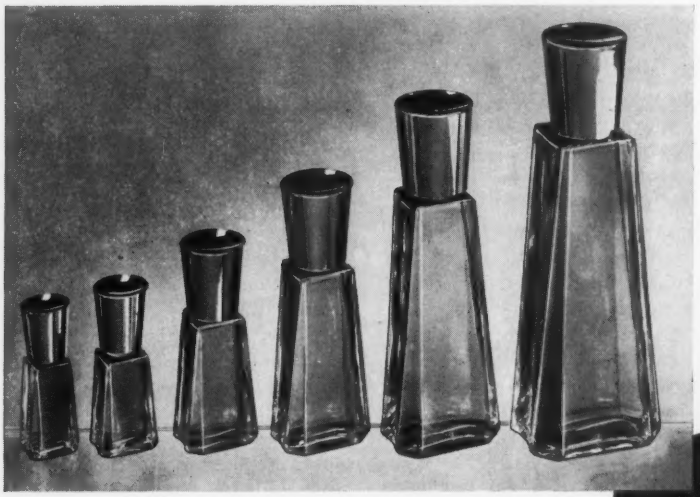
Oral polio vaccine (Sabin Type I strain) facilities at Lederle Laboratories, which expects to produce for the 1961 polio season. This sterile filling line, which is 250 feet long, fills 300 doses of vaccine per minute.

*Paul Klemtner & Company, Inc.

presenting Richford's new

Ambassador

now available with the beautiful Futura Cap in brilliant Goldcote or other finishes



Sizes available: 1½ dram, 2 dram, 1/2 oz., 1 oz., 2 oz., 4 oz.

Now available with the beautiful new Ambassador cap shown here.

Observe the beautifully designed silhouettes of the new Ambassador perfume bottles and the perfect blending of the caps. You can understand our enthusiasm when you consider that each beautifully designed Ambassador is fitted with the fabulous SPILL-PROOF feature. Also available in standard open neck finishes.

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Oceanside, N.Y.

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CORPORATION

Showrooms.
Empire State Bldg.
350 Fifth Avenue New York, N.Y.

Patent thoughts and trends

BY THOMAS CIFELLI, JR., PATENT ATTORNEY*

Stable Poliomyelitis Live-Virus Vaccine

While the Salk polio vaccine has without question proved to be a boon to mankind against the dreaded killer and despoiler, poliomyelitis, it has been apparent for years that the original hopes that the disease would be wiped out by this vaccine were doomed to failure. This is not to condemn or criticize the Salk vaccine; it is merely to state the facts.

In recent years, work in this field has been done to develop a live-virus vaccine. It is believed that Dr. Sabin's vaccine has been the first successful one. A recent announcement indicates that the Sabin vaccine has been approved by the U. S. Public Health Service for use in the U. S. A. Another live-virus vaccine that may offer promise is the one developed by American Cyanamid Company. Accordingly, even though the Cyanamid product appears to be eclipsed by the Sabin product, the recent issuance of a patent to this company is believed to be of considerable importance. Reference is made to U. S. Patent 2,946,724, based on an invention of William Valentine.

The Valentine vaccine deals with a free-flowing granular vaccine comprising nonpathogenic poliomyelities virus and gelatin, and is administrable orally.

"Poliomyelities virus has been adapted to grow and made nonpathogenic through the use of various known media such as chick embryo, rodent brain, rodent spinal cord, tissue culture, etc. Generally, it can be said that the activity of the virus is stable under freezing conditions in the presence of moisture and that activity stability decreases as the temperature is increased. At about 40° C., for example, the poliomyelitis virus usually dies in about 3 days. At ordinary refrigerating temperatures (4° C.), the activity of the virus is less stable than under freezing conditions. Moreover, although stable when frozen, the poliomyelitis virus is essentially inactivated during a freeze-drying process."

To overcome these difficulties, various suggestions were made with respect to media for suspending the poliomyelitis virus. Polyethyleneglycol was tried, and the combination was then filled and put into gelatin capsules. However, it was found that the virus lost activity in the medium, upon standing for about a month. Attempts to use glycerin were unsuccessful because it liquified the gelatin shell. Also, live poliomyelitis vaccines have been administered orally by adding to milk a suspension of the virus after thawing from the frozen state. The disadvantage of all of these methods was that they required formulation immediately before administration because of the instability of action of the virus if allowed to stand in the various media.

Valentine claims to have found that a suspension of any other known types of poliomyelitis virus in their propagation media can be combined with nonhydrated gelatin to produce a hydrated, free-flowing, encapsulable, particulate, granular poliomyelitis virus vaccine, the virus activity of which remains stable over an extended period of time. It is thus possible to produce an oral poliomyelitis vaccine in large quantities, which need not be made up immediately at the time of administration. The virus activity is said to be stable at both room temperature and at ordinary refrigeration temperatures, that is, from about 4° to about 20° C., for periods of several months.

"In formulating the vaccine of the present invention, a propagation medium containing an attenuated poliomyelitis virus is blended with the gelatin by agitation. During agitation, the gelatin becomes hydrated with the virus-containing propagation medium and the virus is absorbed by the gelatin. During hydration, the vaccine evolves from an initial thin paste to a vaccine consisting of discrete particles when hydration is complete. The vaccine thus produced is a free-flowing, granular one which contains throughout a substantially uniform distribution of the virus.

"Any known virus-propagation media may be used for the purposes of this invention. Examples of these are chick embryo, rodent brain and spinal cord (e.g. those of the hamster, cotton rat, mouse, rat, etc.), tissue culture, etc. The virus is propagated in any of the known media in a non-pathogenic form, and the resulting suspension of the virus in water, along with the tissue, salts, antibiotics, anti-fungal agents, etc. containesd therein, are collected and compounded with the gelatin as described above. The attenuated nonpathogenic poliomyelitis virus used in this invention may titer from 10^1 to 10^9 doses of virus per cc. In practice, it will generally titer between about 10^3 and 10^8. The titer of the preferred oral virus dose ranges between about 10^4 and 10^6. The poliomyelitis virus, after propagation in the tissue culture medium of the following examples (virus medium No. 1), usually titers about 10^5 to 10^9, the preferred titer for oral dosage being obtained by dilution. After propagation in the rodent brain and spinal cord medium of the following examples (virus medium No. 2), the poliomyelitis virus usually titers between about 10^3 and 10^6.

"Gelatin with a particle size of between about 10 to 140 mesh (U.S. standard sieve size) may be used for the purposes of this invention. Gelatin having a particle size of from about 60 mesh to 100 mesh is preferred. Various antibacterial agents and anti-fungal agents may be added to the virus-containing medium prior to its formulation with gelatin. For example, it has been found preferable in the present invention to utilize glycerine, one of several hexahydric alcohols (e.g. sorbitol, dulcitol, mannitol, etc.), nystatin, B

*Richards and Cifelli, Newark 2, New Jersey.

naphthol, mixtures of the methyl and propyl esters of parahydroxy benzoic acid (i.e. a mixture consisting of 1 to 5 parts by weight of the methyl ester to 1 part by weight of the propyl ester), and mixtures of any of these anti-fungal agents with the virus and its propagation media. For example, it is preferable to add nystatin or some equivalent agent to the medium utilized to propagate the virus prior to incubation; after incubation and prior to combining with the gelatin, glycerine or some equivalent agent is added. Examples of antibacterial agents which have been used are penicillin, tetracycline, chlortetracyline, streptomycin, etc. These antibacterial and antifungal agents are absorbed along with the water, virus, etc. contained in the virus-containing media during hydration of the gelatin. The resulting free-flowing granular vaccine may be encapsulated in either soft shell gelatin capsules or hard shell gelatin capsules utilizing conventional apparatus and procedures. Various known excipients may be added prior to encapsulation to further enhance the free-flowing characteristic of the vaccine of the present invention. For example, starches such as potato starch, milo starch and corn starch have been utilized with the present invention in order to better facilitate encapsulation in soft shell capsules."

Two of the Examples taken from the patent are reproduced below:

Example 1

The following is a description of (1) a typical preparation of a tissue culture medium and its use in growing Type I (SM strain), Type II (TN strain), or Type III (Fox strain) poliomyelitis virus and (2) a typical preparation of mouse brain and spinal cord medium and its use in preparing attenuated poliomyelitis virus of the same types and strains as set forth in (1) above. These media will be referred to in the examples that follow as virus-containing medium No. 1 and virus-containing medium No. 2, respectively:

(1) *Virus-containing medium No. 1*

A. Growth of monkey kidney cells (see volume 2, Virology, August, 1956, pages 575 and 576).—Kidneys removed from Rhesus or Cynomolgus monkeys are chopped into small particles and digested overnight (about 15 hours) at 4° C. with 0.25 per cent solution of trypsin and viable cells are recovered therefrom. Approximately 150,000 of these cells per cc. are suspended in a tissue culture medium consisting of:

Bovine serum ultra filtrate	15 volumes.
Hank balanced salt solution	80 volumes.
Beef embryo extract	5 volumes.
Penicillin	50 units per milliliter of fluid.
Streptomycin	50 micrograms per milliter of fluid.

Hank balanced salt solution:

	per 1000 ml. of water
NaCl	8.0 g.
KCl	0.4 g.
$CaCl_2$ (anhydrous)	0.2 g.
$Mg.SO_4.7H_2O$	0.2 g.
$Na_2HPO_4.2H_2O$	0.06 g.
KH_2PO_4	0.06 g.
Glucose	1.00 g.
$NaHCO_3$	0.35 g.

The resulting cell suspension is dispensed into one-liter Povitsky bottles and incubated at 37° C. At the end of six days, the cells have adhered to the glass containers and have grown to form a complete sheet of cells on the bottom of each container.

B. Growth of the virus.—At the end of the sixth day, the fluid content of the tissue culture medium is removed from each bottle and replaced with 500 milliliters of tissue culture Medium No. 199 (see "Reagents and Media for Tissue Culture and Virus Propagation," published by Difco). The contents of each bottle is then seeded with 5 milliliters of attenuated poliomyelitis virus (see volume 162 of the Journal of the American Medical Association, December 1, 1956, page 1281). The seeded medium and cells are then incubated at 37° C. When substantially all of the cells are destroyed (i.e., they no longer adhere to the glass), the fluid medium and the cellular debris are harvested. This usually takes place at the end of four days. After harvesting, the harvested virus-containing medium No. 1 is tested for potency by titration in tissue culture tubes. It may then be combined with gelatin to form a granular free-flowing vaccine described above. However, if preferred, it may at this time be frozen and stored until it is desired to compound it with gelatin.

(2) *Virus-containing medium No. 2*

Swiss Albino mice are each inoculated with 0.03 milliliter of attenuated virus by the intra-cerebral of intra-spinal route. When the mice become paralyzed, the brains and spinal cords of each are harvested. A 20 per cent weight/volume suspension is then prepared of the harvested brains and cords in normal saline solution to which is added 50 micrograms of streptomycin per milliliter of fluid and 50 units of penicillin per milliliter of fluid. This is virus-containing medium No. 2, and like virus-containing medium No. 1 described above, it may then be compounded with gelatin or it may be frozen and stored until it is desired to use it.

Example 2

A Type I (SM strain) poliomyelitis virus vaccine was formulated containing the following components:

Gelatin (60-80 mesh, U. S. standard sieve size)	gms...	50
Corn starch	gms..	13
Virus-containing medium No. 1	cc...	37.5
Glycerine	cc...	37.5

Virus-containing medium No. 1 and the glycerine were combined to form a virus suspension. Both the suspension and the gelatin were then cooled separately in ethanol-Dry Ice baths before blending to about 4° C. The gelatin was then sponged with the virus suspension at about 4° C. with agitation to form individually hydrated particles. The corn starch was then blended into this composition with agitation.

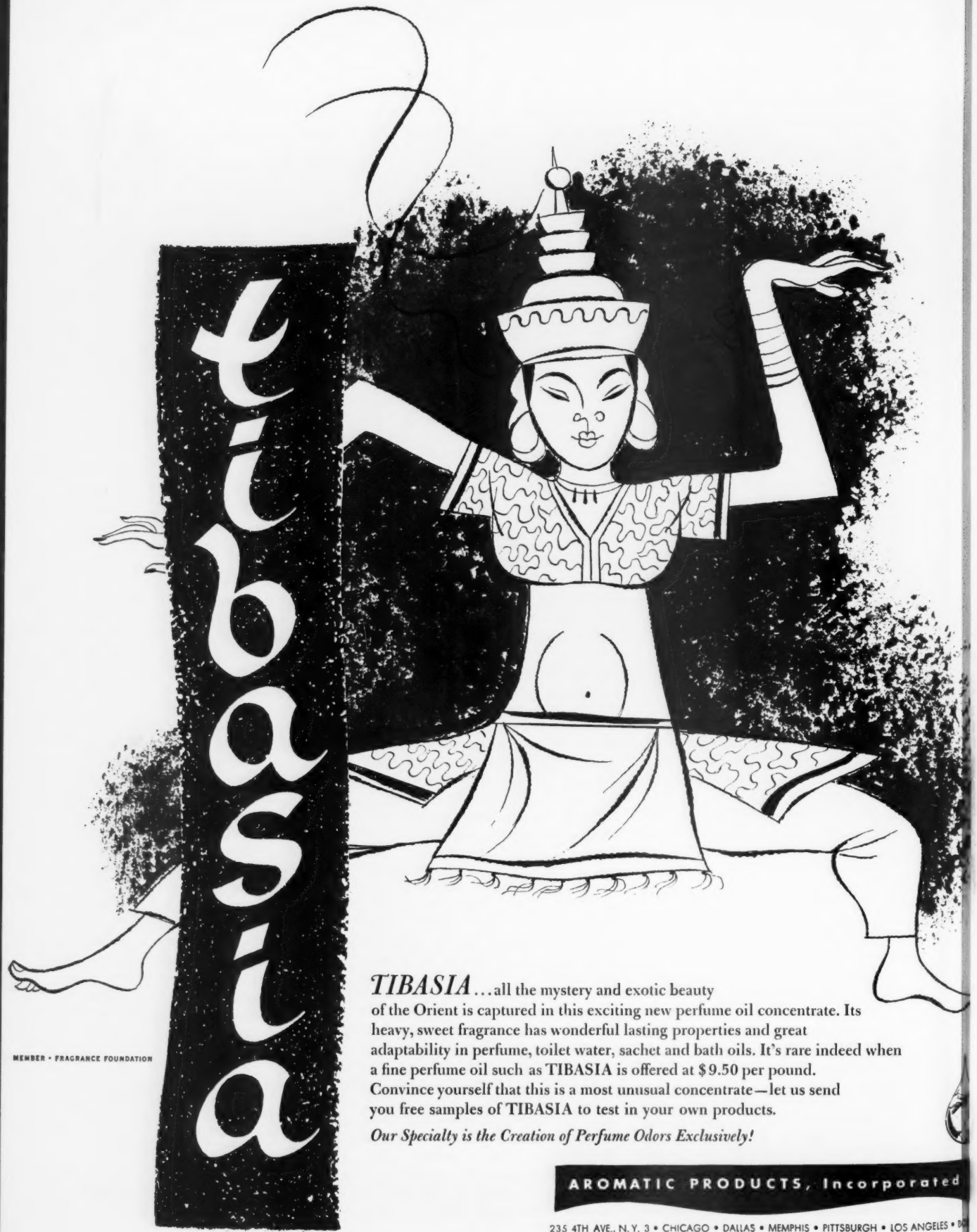
The hydrated, free-flowing, particulate, granular vaccine thus produced was then encapsulated in hard shell gelatin capsules and their potencies evaluated. Representative results of such evaluations appear below:

TITER OF VACCINE ACTIVITY

Temp.	Initial	Times in Days 1	7	13
27° C.	$10^{-4.3}$			$10^{-4.8}$
+4° C.	$10^{-4.3}$	$10^{-4.8}$	$10^{-4.8}$	$10^{-4.2}$
−15° C.	$10^{-4.3}$			$10^{-5.2}$

An idea of the scope of protection

(*Continued on page 561*)



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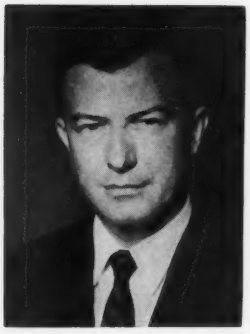


From left to right: Richard H. McCarthy, Jr., vice-president in charge of sales for Bradley-Sun Division, American Can Company; Fred A. Coe, Jr., who has been elected executive vice-president, Burroughs Wellcome

& Co. (U.S.A.) Inc.; Garth H. Quinn, newly elected vice-president in charge of sales, also of Burroughs Wellcome; and Herbert G. Reid, who has joined International Flavors & Fragrances Inc., as controller.

NEWS...

Appointments and Promotions

Richard H. McCarthy, Jr., has been appointed vice-president in charge of sales for the **Bradley-Sun Division, American Can Company.** Mr. McCarthy, director of sales for the past 15 months, joined Sun Tube, a predecessor of Bradley-Sun, as a product manager in 1955. Fenton J. Dowling, a thirty-year veteran with **Canco,** another division, has become western area manager of sales, with headquarters in San Francisco. He joined Canco in 1929 as a laboratory assistant.

Newly elected executive vice-president of **Burroughs Wellcome & Co.** is Fred A. Coe, Jr., formerly vice-president in charge of distribution. He joined the company in 1945, and has been a director since 1952. Garth H. Quinn, general sales manager since 1951, has been elected vice-president in charge of sales. He joined the firm in 1941.

International Flavors & Fragrances Inc. has appointed Herbert G. Reid controller. Mr. Reid was formerly associated with Price Waterhouse and Company.

Joseph V. Kosinski has been promoted to east central district sales manager for the **Flint-Eaton Division, Baxter Laboratories, Inc.,** with headquarters in Detroit. He had been a medical service representative with the firm. Edmond J. Gould has joined Flint-Eaton as northeastern district sales manager. He was formerly with The Central Pharmacal Company. Robert P. Crowner, formerly with Radio Corporation of America, has joined Baxter Laboratories as assistant to E. J. Nawoj, vice-president of manufacturing, and Dr. Robert G. Tucker as manager of scientific services. Dr. Tucker, who served as instructor at Vanderbilt University from 1951 to 1955, has been most recently a senior scientist and group leader with Smith, Kline & French Laboratories.

Robert A. Armstrong has joined **Harshaw Chemical Company** as assistant sales manager of fine chemicals, with headquarters at the Hastings-on-Hudson office. He was formerly with the Goldschmidt Chemical Corporation.

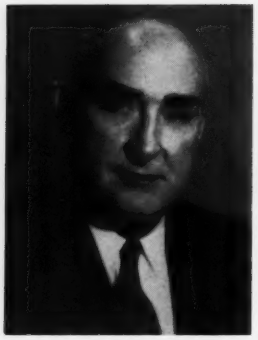
Allen B. Wrisley Company, subsidiary of Purex Corporation, Ltd., has elected Wayne E. Edwards vice-president, manufacturing and research. Formerly Wrisley director of research, Mr. Edwards will now direct manufacturing, research, purchasing, package engineering, quality control, traffic, and warehousing.

Dr. Thomas J. Macek has been named director of pharmaceutical research and development in the **Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc.** He succeeds Dr. Paul W. Wilcox, who resigned recently. Since joining Merck in 1942, Dr. Macek has been closely associated with developing synthetic adrenocortical steroid hormones, synthetic vitamin B_{12}, and antibiotic research. In the **Merck Sharp & Dohme Division,** Don E. Stewart, a former sales representative in Philadelphia, has been named Chicago district sales supervisor, and George H. Nice and Joseph H. Cassell, Jr., have been named to new positions as branch managers. Mr. Nice, formerly Philadelphia branch manager, is now in Chicago, replacing James M. O'Hara, who resigned. Mr. Cassell, who has been assistant branch manager in Columbus, Ohio, succeeds Mr. Nice in Philadelphia.

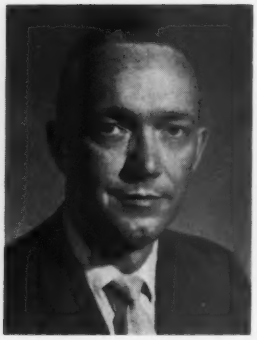
Milton Rosenberg has recently joined the **Geigy Industrial Chemicals Division** customer service department as product manager in charge of surfactants. He had been with Gulf Research.

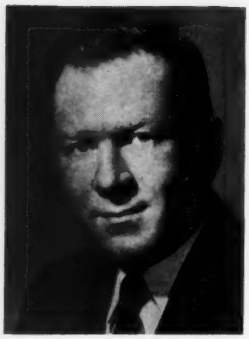
Franklin H. Cooper, who formed Embassy Laboratories, Inc., private-label cosmetic manufacturers, has resigned as secretary-treasurer and been appointed executive director of **Lena Horne Beauty Products, Inc.** Mr. Cooper will have responsibility for the development and design of the entire line. He will continue to serve on the board of directors of Embassy.

Burns Geiger, an associate in education, has been promoted to the position of director of the hospital department, **Roche Laboratories, Division of Hoffmann-La Roche Inc.,** and John N. West to the position of director of education. Mr. West joined Roche as a representative in 1950, and was promoted to division sales manager in Los Angeles in 1958. James Baxter McQuilkin, who has been director of education since 1959, has been named eastern regional sales manager. Mr. McQuilkin joined the company in 1953 as a sales representative, and subsequently became senior assistant to the director of professional service. The **Animal Nutrition Division** has appointed Dr. Charles R. Adams as technical service manager. He was formerly head of large-animal research for Chas. Pfizer & Co. Inc.



From left to right: S. M. Hopkins, president and a director of National Can Corporation; and three at Commercial Solvents Corporation—





Carl F. Prutton, a director, Frank E. Maple, sales manager, nitroparaffins department, and R. A. Mohrman, manager, pharmaceutical sales.

S. M. Hopkins has been elected president and a director of the **National Can Corporation,** replacing J. B. Wharton, Jr., who recently resigned. At the same time, Robert Stuart, Harry N. Eidswick, and Frank O'Brien, Jr., were elected vice-presidents. Mr. Hopkins has been with the company since National Can acquired Pacific Can, of which he was vice-president in charge of sales, in 1955. Mr. Stuart, senior vice-president, joined National with the acquisition of Cans, Inc., in 1952. Mr. Eidswick, financial vice-president and treasurer, also began with the company when Pacific Can was acquired. The vice-president for manufacturing, Mr. O'Brien, has had wide experience in production and management in the industry.

Commercial Solvents Corporation has elected Dr. Carl F. Prutton to the board of directors. He is a director of Food Machinery and Chemical Corporation, from which company he recently retired as executive vice-president, Chemical Divisions. He was formerly vice-president, director of operations, engineering, and research for Mathieson Chemical Corporation. Commercial Solvents has created a separate marketing department to handle nitroparaffins, with Frank E. Maple as sales manager. Mr. Maple, closely associated with nitroparaffin development for 20 years, was formerly sales manager of the company's industrial chemicals sales department. Finally, Robert A. Mohrman has been named manager of pharmaceutical sales. Mr. Mohrman joined the company in 1953; most recently he has served as assistant to the sales manager of the industrial chemicals department.

Richard M. Mace has been appointed to the newly created position of new products manager by **E. R. Squibb & Sons.** Mr. Mace has been with Squibb since 1948, becoming sales manager for Squibb in Canada in 1956.

Stanley A. Merrill, vice-president of sales since 1957 of **Purepac Corporation,** has been appointed a director. He joined the concern in 1946 as a salesman, and was promoted in 1951 to general sales manager of American Druggists Syndicate, a subsidiary. He later became assistant general sales manager of the parent company.

Crown Cork & Seal Company has appointed Edward Stern to the newly created position of director of marketing. Mr. Stern has been with Charles E. Hires Company, serving in a variety of positions, most recently as vice-president in charge of carbonated sales.

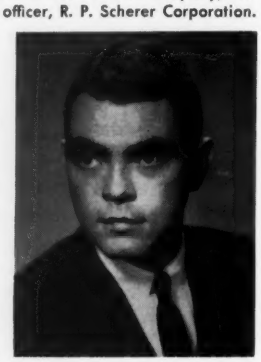
Robert P. Scherer, Jr., has been appointed chief executive officer of the **R. P. Scherer Corporation,** with the title of executive vice-president and general manager, succeeding his late father, the founder of the company. Mr. Scherer has been actively associated with the company since he completed his studies in engineering and business administration at Northwestern University and the University of Michigan.

James A Carvis has been promoted from assistant buyer to buyer in the packaging materials division of the purchasing department of **Abbott Laboratories.** Mr. Carvis joined Abbott in 1948.

Newman-Green, Inc., has appointed Fred B. Ducey as sales correspondent, responsible for customer inquiries and general sales liaison.

From left to right: Richard M. Mace, new products manager, E. R. Squibb & Sons; Stanley A. Merrill, a director, Purepac Corporation;

Edward Stern, director of marketing, Crown Cork & Seal Company; and Robert P. Scherer, Jr., chief executive officer, R. P. Scherer Corporation.



From left to right: Frank W. Abernathy, district sales manager for the Chemical Division, Eastman Chemical Products, Inc.; Dr. M. M. Gladstone, manager, Emcol Division, Witco Chemical Co.; Harold M. Roman, general manager, operations, A. H. Robins Company of Canada, Ltd.; and Francis J. Regulski, who has been promoted to the position of plant manager of the pharmaceutical laboratories division, Schieffelin & Co.

Frank W. Abernathy has been named a district sales manager for the **Chemical Division, Eastman Chemical Products, Inc., subsidiary of Eastman Kodak Company,** and will direct sales of industrial and specialty chemicals in the New England area from offices in Framingham, Mass. Mr. Abernathy has served in the New York sales office as a sales representative for the past five years.

Dr. M. M. Gladstone has been promoted to manager of the **Emcol Division, Witco Chemical Company's Organic Chemicals Division.** He had served as assistant technical director of Witco's Organic Chemicals Division. He has been with Witco and Emulsol, a Witco acquisition, for 20 years.

General manager of operations for the **A. H. Robins Company of Canada, Ltd.,** is Harold M. Roman of Ontario. He has been western division sales manager for the Canadian firm. Mr. Roman moves to Montreal, where Robins is constructing a new plant and research laboratory.

Francis J. Regulski, formerly with Merck & Co., has been appointed plant manager of the pharmaceutical laboratories division of **Schieffelin & Co.** Mr. Regulski has also been associated in a production capacity with Ortho Pharmaceutical Corporation.

Hazel-Atlas Glass Division of the Continental Can Company has announced the combination of its Cincinnati, Ohio, and Louisville, Ky., sales districts into one, with headquarters at 617 Vine Street, Cincinnati. H. Carman Crago, formerly district sales manager in Cleveland, is manager of the new district. J. Edwin Porter, formerly district sales manager in Louisville, is now executive sales representative in that city, and Sheldon W. Keller is office manager in Cincinnati. The Pittsburgh and Cleveland districts have also been combined, with headquarters in Pittsburgh, under the management of John S. Auvil.

The **Flint-Eaton Division, Baxter Laboratories, Inc.,** has promoted two: Bruce G. Molloy, formerly assistant to the president of Wallerstein, is now New York district sales manager; and Alvin M. Toral, a medical service representative, is now Chicago district sales manager.

Dr. Richard J. Manner has joined the clinical research department of **Mead Johnson & Company** as associate director. Dr. Manner has spent the last five years in private practice in Rochester, N. Y., where he was also industrial physician with Stecher Traung Lithograph Corp.

H. Courtney Smith, formerly divisional sales manager in Washington, D. C., for Arthur S. LaPine & Company, has joined the sales staff of the **Glass Products Division, Fischer & Porter Company,** manufacturers and distributors of laboratory supply equipment. Mr. Smith will serve as sales representative in the Atlanta, Georgia, area.

Cutter Laboratories has named Dr. Stanley Ellis research chemist in the protein section of chemical research. Dr. Ellis has a wide background in biochemistry research, serving most recently as assistant professor of biochemistry at Emory University, Atlanta, Ga., during which time he also directed the preparation of anterior pituitary hormones for the Endocrinology Study Section of the National Institutes of Health.

Dr. Frank Rupp, Jr., has been appointed to the **Colgate-Palmolive Company's Biological Research Laboratories,** New Brunswick, N. J. He will work in microbiology. The company has also appointed Dr. Sam Yankelowitz to the staff of the **Oral Health Research Laboratories,** in the field of biochemistry.

The **Puritan Aerosol Corporation** has named Theodore A. Thonet as research director. Mr. Thonet had been associate research director.

New merchandising manager for the **Pepsodent Division of Lever Brothers Company** is Richard E. Baiter, who formerly served in the Lever Division as merchandising manager for toilet soaps.

Kenneth Branford, field supervisor for Los Angeles, and Joseph Gaidzik, northern California district manager, have been elected vice-presidents for **Formula 42 Products.** Both are in their sixteenth year with the firm.

F. Leonard Bryant, a vice-president of **Hooker Chemical Corporation,** has been elected executive vice-president and a director. Also elected directors are Thomas F. Willers, a Hooker vice-president, and Werner P. Gullander, executive vice-president and a director of General Dynamics Corporation. Mr. Gullander fills the vacancy created by the resignation of E. Lewis Burnham, a Hooker director since 1924. Mr. Bryant and Mr. Willers are also on the executive committee of the board of directors. Mr. Bryant has been with the company since 1935, Mr. Willers since 1941, and Mr. Gullander since early this year.

KESSLER

FATTY AND DIBASIC ACID ESTERS
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From left to right: Elizabeth Heitner, assistant to the president of Pharmacraft Laboratories; Dr. C. Paul Hegarty, manager of the virology section of the research division, Wyeth Laboratories; Patrick H. Seay, assistant director of research and director of biological research at McNeil Laboratories; and J. K. Shea, who has been promoted to the position of sales manager with the Peterson Filling & Packaging Co.

Pharmacraft Laboratories has promoted Elizabeth Heitner from the position of secretary to the president to that of assistant to the president, and Robert E. Bakon, sales analyst, has been promoted to sales service manager. Miss Heitner has been a member of the organization since 1959, prior to which she was with the parent company, Joseph E. Seagram & Sons, Inc. Alan E. Woltz has been promoted to general sales manager from assistant general sales manager. He joined Pharmacraft in 1956 as a district sales representative.

Dr. C. Paul Hegarty has been appointed manager of the virology section in the research division of **Wyeth Laboratories.** Dr. Hegarty had been director of biological development and control with Merck Sharp & Dohme.

Patrick H. Seay, Ph.D., has been appointed assistant director of research and director of biological research at **McNeil Laboratories.** Dr. Seay has been for nine years a senior researcher in pharmacology with The Upjohn Company. Five professional service representatives have joined the sales staff: Charles L. Arnold, Jr., James V. Emholz, Jack H. Sullivan, Max Graff Walten, Jr., and Ray M. Wilson. Mr. Arnold will cover the Roanoke, Va., area; Mr. Emholz, Minneapolis, Minn.; Mr. Sullivan, Indianapolis, Ind.; Mr. Walton, Pittsfield, Mass.; and Mr. Wilson, Albuquerque, New Mexico.

The **Peterson Filling & Packaging Company** has promoted J. K. Shea from eastern sales manager to sales manager and William L. Rowley from plant superintendent to plant manager, and has appointed Larry Ligocki to the newly created position of chief machinist. Mr. Rowley replaces Mr. Hegeler, who has assumed full-time duties as treasurer. Mrs. Marie Lambert has been appointed to the filling research staff.

Four new vice-presidents have been appointed by **Union Carbide Chemicals Company, Division of Union Carbide Corporation:** Richard F. Brown, vice-president, sales; Robert L. Duncan, vice-president, product marketing; Thomas R. Miller, vice-president, research and development; and Arthur P. Moss, vice-president and works manager. Dr. George H. Law, vice-president, research, is retiring on November 1. Until then he is serving as special advisor to the president, E. E. Fogle.

Robert E. Lundigan has been appointed to the newly created position of clinical research associate in the medical department of **The Norwich Pharmacal Company.** Mr. Lundigan was formerly the Eaton sales representative in the Los Angeles area. In the company's scientific division, Frank G. Benenati, formerly office manager of the special sales division, has been named to the administrative staff. Mr. Benenati joined Norwich as an organic chemist in 1952.

Melvin W. Kerner, who joined **Schering Corporation** in 1956 as a professional sales representative, has been appointed Charlotte, N. C., divisional sales manager. His field staff covers Charlotte, Asheville, Salisbury, Greensboro, and Winston-Salem, N. C.; Florence, Greenville, Columbia, Charleston, and Spartanburg, S. C.; and Knoxville and Bristol, Tenn.

George Abrams has joined **The J. B. Williams Company, Inc.,** as vice-president, director of corporate development. In line with the firm's expansion plans, Mr. Abrams will concentrate on acquisitions and product development, reporting directly to president M. B. Rosenhaus.

Dr. Ross V. Sayers has been appointed vice-president of **George A. Breon & Company, Division of Sterling Drug Inc.** Dr. Sayers has been medical director of Breon, and continues in that position. He was previously assistant director of medical research for Winthrop Laboratories, a Sterling unit.

Parke, Davis & Company has named Dr. Robert G. Brackett an associate research microbiologist. He has served as a bacteriologist with other pharmaceutical firms.

The board of directors of **Shulton, Inc.,** have elected Richard A. Dey secretary, succeeding Howard Engel. Mr. Dey has been director of industrial relations since 1955. He joined Shulton in 1944.

Philip J. Wagner has joined the **Robinson-Wagner Company, Inc.,** as a sales representative.

Carl A. Setterstrom, formerly general manager of marketing for Avi-Sun Corporation, a firm jointly owned by American Viscose Corporation and Sun Oil Company, has been named vice-president of marketing for the **Rexall Chemical Company, Division of Rexall Drug and Chemical Company.**

Newly appointed vice-president in charge of research and development of the **Lemmon Pharmacal Company** is Dr. Paul W. Wilcox, formerly director of pharmaceutical research and development, Merck Sharp & Dohme Research Laboratories.

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- FRUIT AND NUTRITIVE CREAMS
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Warren Martin Elected

Warren L. Martin, veterinary sales manager for the Eaton Laboratories Division, The Norwich Pharmacal Company, has been elected

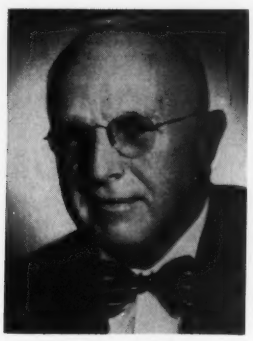
WARREN L. MARTIN

president of the American Veterinary Exhibitors Association. He was formerly secretary-treasurer of the organization.

Dr. Moliter Retires

Dr. Hans Moliter, director of the Merck Institute for Therapeutic Research from its establishment in 1933 until 1956, has retired from his position as director of scientific relations of the Merck Sharp & Dohme Research Laboratories Division.

Dr. Moliter began at the Institute with a staff of two, who were high school graduates. Today, it has a highly qualified staff of 300 scientists and technicians, as well as extensive facilities, including a 200-acre experimental farm. He had come from an associate professorship in pharmacology and therapeutics at the University of Vienna.



HANS MOLITER

Dr. Moliter was elected chairman of the board of trustess of the Merck Institute in 1956, succeeding the late George W. Merck.

Dennis Duveen Receives History of Chemistry Award

Dennis I. Duveen, head of the Duveen Soap Corporation, received the 1960 Dexter Chemical Corporation Award in the History of Chemistry at the recent national meeting of the American Chemical Society. The award, consisting of $500 and a plaque, is sponsored by the Division of the History of Chemistry of the society, and is given each year for outstanding contributions to the history of chemistry.

Mr. Duveen, known as an expert on Antoine Lavoisier, has published almost 100 papers and books, most of them on chemical history.

D&O Man Elected in Canada

John J. Thompson, vice-president of Dodge & Olcott of Canada, Ltd., has been elected associate director of the Toilet Goods Manufacturers Association of Canada for the year 1960-1961.

Justin Powers Retires

Dr. Justin L. Powers, director of revision of the *National Formulary* and editor of the *Scientific Edition of the Journal of the American Pharmaceutical Association* has retired, after 20 years with the association.

Dr. Powers has served on many committees, including advisory bodies of the U. S. Pharmacopeia, the National Research Council, and the World Health Organization.

Norwich Manager Retires

Noble Reeves, manager of Norwich Pharmacal Company's southwestern sales division, has retired.

NOBLE REEVES

With Norwich nearly 25 years, Mr. Reeves began his association in 1936 as representative in San Antonio, Texas.

DCAT Elects Day

James Day, New York district manager of The Dow Chemical Company, was elected president of the Drug, Chemical and Allied

JAMES DAY

Trades Association during the recent menting at Lake George, N. Y.

Named to serve with him are: vice-president, Wm. J. Schieffelin, III, Schieffelin; treasurer, F. M. Schwenner, Pharmaco; counsel, William J. Quinn, Merck; secretary, Helen L. Booth.

Members of the executive committee are: Dr. Benjamin W. Carey, Lederle; Charles O. Hoyt, Carter; Barclay E. Mackinnon, Penick; E. S. Robinson, Monsanto; Herman M. Schulman, Washine; and, reelected for three-year terms, Fred A. Coe, Jr., Burroughs Wellcome; and George A. Holloway, Chesebrough-Pond's.

Our Error

In the July issue of the magazine, in this same section, we inadvertently omitted the photograph of Dr. John J. Burns, associate research di-

JOHN J. BURNS

rector of the Pharmacodynamics Division, Burroughs Wellcome & Co. (U.S.A.) Inc., although his name appeared in the caption.

A MAN REQUIRES SPECIAL TREATMENT!

He appreciates a pleasantly scented product just as thoroughly as does his "so-called" better half. But, generally speaking, he's terrified at the very thought of smelling "perfumy"! He buys *shave creams, soaps and aerosols; talcs and after-shave lotions; hair conditioners, shampoos, tonics and brilliantines; even colognes* . . . but to secure his brand allegiance requires one primary factor. The fragrance used must be one that he will unquestionably identify as *masculine*. To develop such custom-tailored odors demands not only good perfumers and modern equipment . . . but also the invaluable background that comes only with years of practical experience. For more than a century and a half, D&O has been serving the perfumed products industries of the nation with time-tested fragrances. Let our product-development laboratories help you give that sales-winning "special treatment" to your men's toiletries! Consult D&O.

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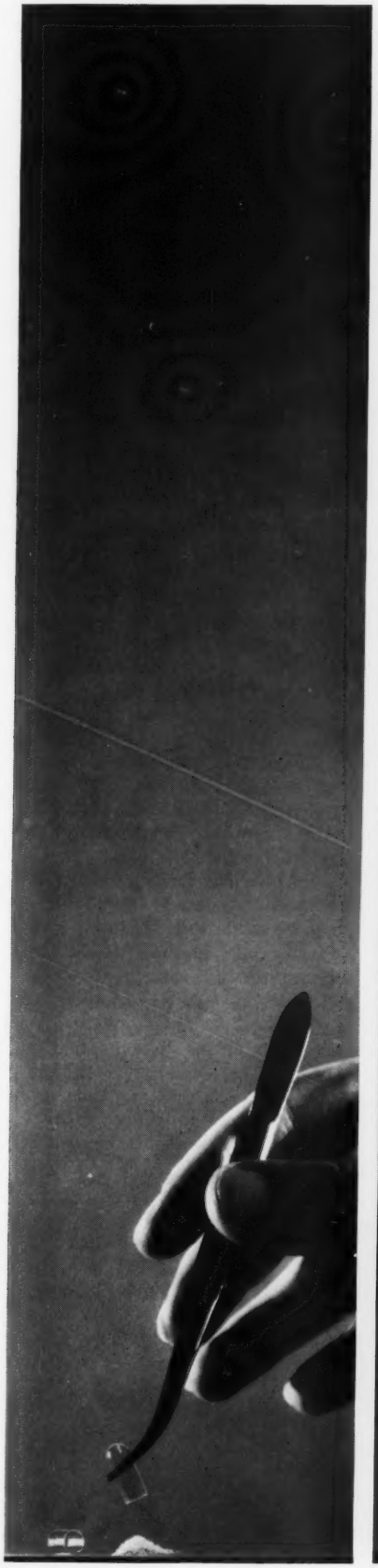

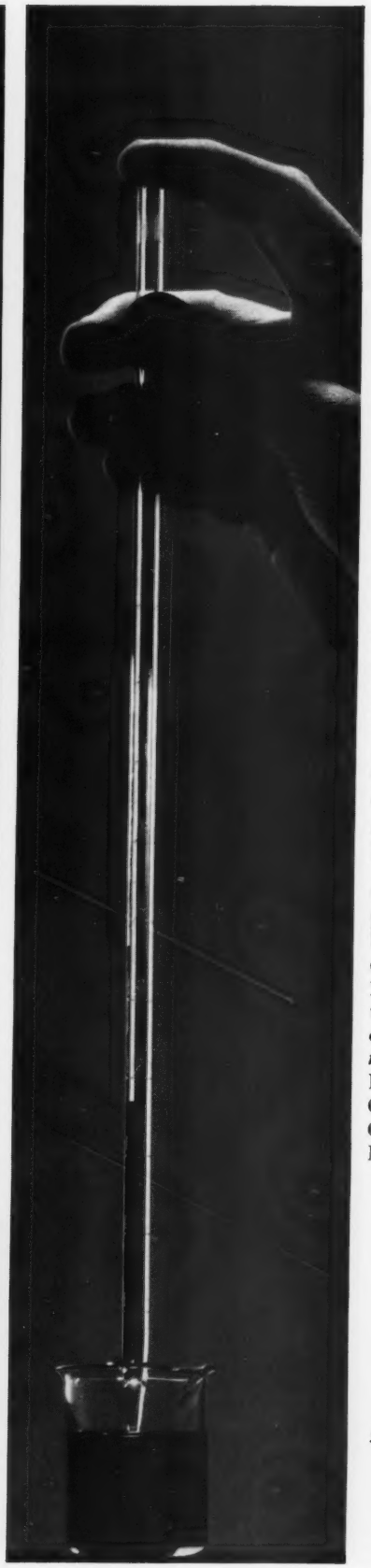

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These are for the pharmaceutical man who wants vitamin E in the most concentrated form there is.

They are the two most potent varieties of vitamin E he can buy. Either makes it easier to incorporate vitamin E in an already tightly packed multivitamin tablet or capsule.

For maximum dosage in minimum oil, there is just one answer, our *d-Alpha Tocopheryl Acetate*, N. F., Type 6-100. It delivers 1360 I. U. of vitamin E per gram, the highest of any commercial preparation.

For tablets and dry-fill capsules, our *Crystalline* d-*Alpha Tocopheryl Acid Succinate N. F.* delivers 1210 I. U. to the gram in a pure, free-flowing, white powder that packs well.

Gram for gram, they outdo in effectiveness even the material on which the present International Standard is based, because they are derived from vegetable oils and contain only the *d*-stereoisomer, 36% more potent than the *dl* combinations. For samples, information, and a quotation, get in touch with ***Distillation Products Industries,*** Rochester 3, N. Y. Sales offices: New York and Chicago • W. M. Gillies, Inc., West Coast • Charles Albert Smith Limited, Montreal and Toronto.

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Also . . . vitamin A . . . distilled monoglycerides . . . some 3800 Eastman Organic Chemicals for science and industry

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Dr. H. W. Hibbott, president of the British Society of Cosmetic Chemists, makes a presentation to Mr. Amsterdam, president of the American SCC, during his visit to England.

Dr. Sobel Receives Ames Award

The American Association of Clinical Chemists presented the 1960 Ames Award to Dr. Albert Edward Sobel for his outstanding contributions to clinical chemistry and to biochemistry; for his work as a scientist; and for his efforts as an individual on behalf of the professional standards of clinical chemistry.

Dr. Sobel has engaged in research and is currently adjunct professor of chemistry, Polytechnic Institute of Brooklyn, N. Y., as well as special lecturer in biochemistry, State University of New York College of Medicine. He is the author of more than 160 papers, primarily in the chemistry of bone and tooth formachemistry, absorption and transportation of fat-soluble vitamins, and tion, development of quantitative ultramicro methods in clinical steroid chemistry.

R. E. Horsey Chosen

R. E. Horsey, vice-president of Givaudan-Delawanna, Inc., has accepted appointment as chairman of the essential oils division of the Travelers Aid Society for New York's annual fund drive.

Eastern PWA Established

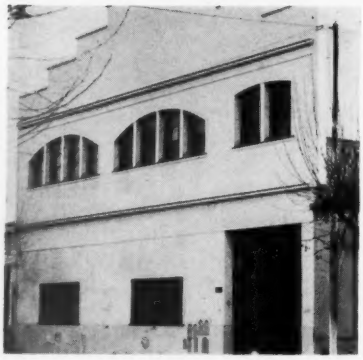
The Pharmaceutical Wholesalers Association has established offices in New York City, in conjunction with its becoming a national organization. The address is 551 Fifth Ave., New York 17, N. Y.

Allstadt Honored

Louis M. Allstadt, director and assistant secretary of George Lueders & Co., Inc., was recently welcomed into the Lueders Twenty-Five Year Club at a luncheon. He was given matching luggage and a watch.

Expansions, Acquisitions, And New Plants

J. T. Baker Chemical Co., and **B. Herzog Comercio E. Industria, S.A.,** of Brazil have organized a joint firm, Baker-Herzog Produtos Quimcos Ltda., with offices in Sao Paulo. President is Max L. Herzog; managing director, John E. Avery, Jr., Baker's present export manager. . . . **Coppertone Corporation,** subsidiary of Plough, Inc., has opened its new building covering 17,000 square feet at LeJune Road, Miami, Fla. . . . A two-year expansion and reorganization of **Smith Kline & French Laboratories'** field force has begun with 28 managerial promotions. By mid-1962, the professional service corps is expected to number



Modern building in Bernal, suburb of Buenos Aires, in which compounding and research operations of Givaudan Argentina S.A. are now conducted. Further expansion is in process.

600, and two new divisions will bring to eight the area offices. . . . Production of a complete line of industrial adhesives has begun at the new **Morningstar-Paisley, Inc.,** plant in Atlanta, Ga. The plant will also serve as a warehouse for other products of the company. . . . The **Rexall Drug Company** has installed a second complete aerosol filling line in its St. Louis plant. . . . **Textron Inc.** has announced formation of Textron Pharmaceuticals, Inc., to engage in the ethical and proprietary drug business. Robert E. Grant, financial vice-president of Plough, Inc., is president, with headquarters in Providence, R. I. . . . **Old Empire** has acquired the facilities of Garde Drug Co. Inc., of Philadelphia, which expands the firm's facilities for packaging pharmaceuticals. . . . **Suppositoria Laboratories, Inc.,** has acquired Crayton Laboratories of New York City. The Crayton plant has been moved to Farmingdale, N. Y., for consolidation with Suppositoria. . . . **Aluminum Company of America** has expanded its Richmond, Ind., works for the third time in three years.

Officers and directors of the American Society of Perfumers meeting at the invitation of President Polak, at the Middletown Country Club to discuss the society's fall activities; left to right: seated, Dr. Anthony Frascati, Mrs. Dorothy Douglass, Dr. Oliver L. Marton; standing, Bernard Polak, John Hancock, Herbert Summer, and Edward J. Shuster.

Merrell Inaugurates Quarter Century Club

A new Quarter of a Century Club has been inaugurated by the Wm. S. Merrell Company in recognition of employees with 25 years or more of service. Charter members who received certificates included the following executives: Nelson M. Gampfer, chairman of the board; Frank T. Jacobs, vice-president; Dr. R. S. Shelton, vice-president; William J. Ransom, treasurer-comptroller; and Herman W. Schuster, assistant treasurer-comptroller.

New Buffalo Office for Eastman Chemicals Division

The Chemicals Division of Eastman Chemical Products, Inc., subsidiary of Eastman Kodak Company, has established a new office in the Snyder Square Building, 4498 Main Street, Buffalo, N. Y., under George O. Trabue, for western New York, Pennsylvania, southern Ontario.

HNI Office Moves

The offices of the Health News Institute have been moved to 1411 K Street, N.W., Washington 5, D. C.

High School Students Visit Hoffmann-La Roche Plant

Twenty-five science students from Glen Rock High School, Glen Rock, N. J., recently took part in a two-day science course conducted by Hoffmann-La Roche Inc. at its Nutley, N. J., plant. Scientists of the firm's research staff lectured and led discussions in psychopharmacology, pharmacology, and chemotherapy.

Among the speakers were Dr. George A. Heise, Dr. Robert A. Moe, Dr. E. John Lynch, Dr. Herbert N. Prince, and Dr. Emmanuel Grunberg. Laboratory sessions were conducted by technicians in the Roche chemistry department.

New Fleuroma Plant Opened

Fleuroma, Inc., is now occupying a new plant at 43-23 Dreyer Avenue, Long Island City 1, N. Y.; telephone: RAvenswood 1-8282.

Extensive renovations have been in process since early this year, including modern perfume laboratories and aromatic chemical manufacturing facilities. The new plant provides for further expansion, for which plans are now under way.

Fleuroma's new plant on Dreyer Avenue in Long Island City, New York, which is now on stream.

Ernest Goodpasture

Dr. Ernest W. Goodpasture, former Dean of the Vanderbilt University Medical School, died September 20 at the age of 73.

In 1931, while a Professor of Pathology at Vanderbilt, Dr. Goodpasture devised the idea of using embryos from live chickens for cultivating viruses to be used in a vaccine for mumps. Although little publicized, it later made possible the immunization of thousands of American soldiers against many diseases in World War II. Dr. Goodpasture refused to patent his procedures.

Dr. Goodpasture conducted research and taught in several well-known medical schools and hospitals before he returned to Vanderbilt, from which he had graduated, in 1907. He was Dean of the Medical School there from 1945 to 1950.

From 1955 until his retirement last year Dr. Goodpasture was scientific director of the Department of Pathology of the Armed Forces Institute of Pathology at the Walter Reed Army Medical Center in Washington, and served publically and privately in a number of other ways.

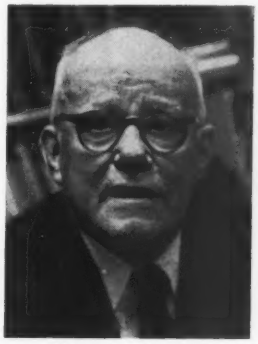
Mark Biddison

Mark M. Biddison, former president of the General Chemical Division of the Allied Chemical Corporation, died September 18 in Sarasota, Florida, where he had lived since his retirement in 1957. He was 68.

Mr. Biddison joined the division's sales department in 1918, later becoming manager of the Cleveland office, and divisional sales manager. Appointed assistant general manager in 1934, he became general manager thereafter, and, in 1947, vice-president.

Harry C. Phibbs

Harry C. Phibbs, founder of the Harry C. Phibbs Advertising Company, died September 12 at his home in Winnetka, Illinois.



HARRY C. PHIBBS

When Mr. Phibbs founded his agency in 1921, no agency had devoted itself exclusively to the promotion of ethical pharmaceuticals and to the dental and medical professions.

Prior to starting his own agency, Mr. Phibbs had been sales and advertising manager of Burroughs Wellcome & Co. (U.S.A.) Inc., and had acted as special consultant on campaigns for Vick Chemical Company and other leading concerns.

Mr. Phibbs, who was born in Dublin, Ireland, was a charter member and one of the first directors of the Midwest Pharmaceutical Advertising Club.

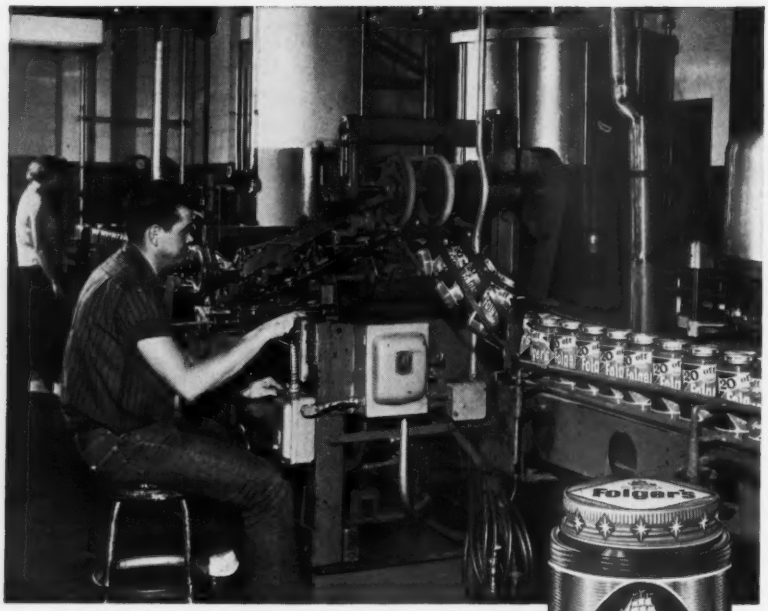
Carl Nielsen

Carl Nielsen, retired director of Abbott Laboratories, died August 31 in San Francisco, California. He was 80 years old.

He was active at Abbott for 34 years before his retirement in 1946, at which time he was associate director of research and director of nutrition and pharmaceutical research. He served as a member of the board of directors from 1934 to 1946.

Born in Copenhagen, Denmark, Mr. Nielsen was first employed in Europe for several years in prescription pharmacy and laboratory work. In 1908 he was engaged by the Department of Agriculture of Mexico to study byproducts of the henequen grown in Yucatan. When his work was interrupted by the revolution of 1911-1912, he joined Abbott.

Mr. Nielsen was made a Knight of the Order of Dannebrog, in 1948, by Frederick IX, King of Denmark.



Dry air speeds packaging ...protects quality of instant coffee

Instant coffee absorbs moisture fast. If this happens before it reaches the coffee cup—say when it's being packed—it can clog up packaging machines, ruin the quality of the coffee. In Houston, where humidity stays high for long stretches, the makers of Folger's coffee solved the problem by installing a Lectrodryer that keeps relative humidity at 25% to 35%.

Controlled dryness by Lectrodryer has been the answer to many problems caused by moisture; gumming up of hygroscopic powders, corrosion of metal, air line freezeups, and contamination of drugs, chemicals, liquids, gases.

Lectrodryer Type CHO-1500 dries recirculated and make-up air at the Folger plant.

For a Guide in Planning your own drying system, write for Lectrodryer's Case History Sheets, which give details on how many of these problems were solved. Tell us where you're having trouble with moisture. Pittsburgh Lectrodryer Division, McGraw-Edison Company, 309 32nd Street, Pittsburgh 30, Pennsylvania.

Management Forum

BY FRANCIS CHILSON, Sc.D.
ENGINEERING CONSULTANT

Literature Research

An enormously important phase of research and development is literature and patent research. Millions of dollars of research money has gone down the drain because this sort of research was not done adequately before costly commitments were made. An official of American Cyanamid estimates that ten per cent of the money spent in research is wasted because of inadequate literature and patent research. Many companies have had the frustrating experience of bringing a product almost to the marketing stage, only to learn that it had been patented several years before by one of its competitors.

A patent is meaningless until it has been tested in the courts. I have often been impressed with the extent of the research done by patent examiners when they cite prior patents bearing upon the patent application one may be interested in. (I should know! Every time I think of a brilliant, patentable idea, I find in the response of the patent examiner that seven million other guys had the same idea.) But the fact that a patent is issued is no guarantee that, somewhere in the patent office under different file classifications, or somewhere in the literature, there is no patent or publication that nullifies your idea.

And the problem of patent and literature research is increasing to an incredible degree. There are in the world upwards of *one hundred thousand* technical journals and God knows how many millions of technical books and patents issued by our own and foreign countries.

Such an innundation has flooded our libraries and overwhelmed our librarians. Such a flood had to be coped with somehow. So IBM, Eastman Kodak, and many others went to work on it. Kodak developed a system of miniscule photography that reduces documents to the size of a pin head. Scientists of the Bureau of Standards have developed a camera that can reduce the entire 24,000 pages of the Encyclopedia Britannica to an area the size of a match book. Along with miniscule photography, magnetic tape-recording systems have been developed for coding and recovering needed references. This procedure is known as information retrieval and already there are information retrieval consultants in the field! A proposal has been put forth to establish centralized, mechanized centers, which, for a consideration, can produce pertinent information from any source in the world. There is a center like this in Moscow. It is called VINITI. This center reviews more than 12,000 journals, and abstracts half a million articles. VINITI means All Union Institute of Scientific and Technical Information. Bell Telephone is working on machines to code, file, and abstract information. There are 15 or 20 firms working on various types of equipment to miniaturize, file, abstract, enlarge, and read scientific information.

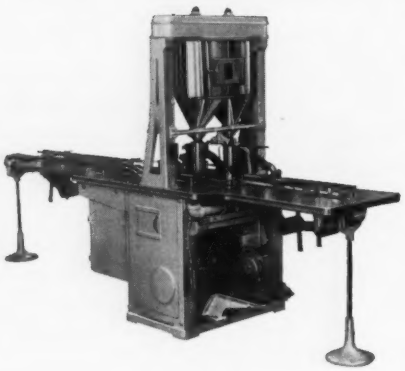
Man's scientific knowledge is increasing so rapidly that the time may come when patent protection may have to be abandoned altogether because it will be impossible to think of anything truly novel.

Management Problems

It really is very difficult to write—or speak—to a group on such a general subject as management. A similar difficulty is encountered in talking to a group of engineers on the subject of engineering, as I found out last Spring when I addressed the engineering and production section of the PMA. The reason for this is the diversity of one's audience. Such an audience is compounded of neophytes, or persons midway on the journey to success or failure, as well as of those who have arrived and are in fact important officials of their companies. For example, in my audience last Spring I had men who were not merely production men or engineers but also vice-

FMC Auger Fillers meet high-quality standards for Chesebrough-Pond's

Chesebrough-Pond's Inc., has long been well-known in the cosmetic industry for products of the highest quality. For many years they have used FMC Auger Fillers to meet the high standards they maintain for their powder and talc products. Ten FMC automatic and semi-automatic fillers of three different types fill a wide variety of sizes and kinds of containers from gold-finished metal canisters to lithographed paperboard drums.



The Duplex Auger Filler model HG-84 is one of the FMC units installed at the Chesebrough-Pond's plant in Clinton, Connecticut. Completely automatic, this model is designed with a choice of filling methods—cam volumetric, gross weighing, or auger combined with vacuum for pack filling dusty products—at speeds up to 70 containers per minute. Many other models are available for large or small plants, automatic or semi-automatic operation, tight or loose fills, long or short runs to handle powders, granules, and certain pastes. Production run accuracy has proved outstanding in filling cans, jars, boxes, bags, etc. from ½ oz. to 20 lb. Changeover for product and size is exceptionally fast and simple. Speeds as high as 140 per minute.

Putting Ideas to Work

FOOD MACHINERY AND CHEMICAL CORPORATION

FMC Packaging Machinery Division

Stokes & Smith Plant

4912 SUMMERDALE AVENUE, PHILADELPHIA 24, PA.

For the whole story of how FMC Auger Fillers can improve your packaging, write for Bulletin P-811.

presidents and directors of their companies. I also had young men one or two steps up on the management ladder, and a substantial group who were half way up.

Now, the problem is one of communication. If one chooses to be specific or didactic, his suggestions may be new to one group and old hat to another. So, in this essay on management I shall try—and probably fail—to dig up a few notions about the practice and philosophy of management that may be new to a few of you.

First of all, it must be admitted that the success and opulence of this country's economy is not entirely due to the brilliance and vision of the administrators and managers of our businesses. We, all of us, are riding on the up-surging tide created by our wealth of natural resources. That's what made this country wealthy and great.

Suppose we didn't have the natural resources, how would we stack up against our competitors in the international field? Some of the largest and most profitable companies in the world were created in Japan, Switzerland, Italy, England, and West Germany. Some of these countries have no natural resources at all, apart from a bit of coal or a bit of iron, so the conclusion must be drawn that, since these countries suffer the disadvantage of having to import virtually all their raw materials and export virtually all their finished goods, their administrators and managers must be far more capable as a group then ours. Both Japan and Germany have risen like the Phoenix from the sere ashes of their burned-out economies to the very zenith of industrial success. Some of you will say "Why the hell shouldn't they; they have a plethora of cheap labor!" But cheap labor is not by any means the whole answer or even the most important part of the answer. In England, Germany, and Switzerland, labor rates are rising rapidly. In Switzerland—one of the richest countries in the world—it is necessary for businessmen to import, not only all raw materials, but also labor, to the tune of some five hundred thousand persons per annum from Italy. France, Austria, and Germany, in order to keep their factories going. How would you like to carry on under those circumstances?

We have created vast international markets for many of our products such as automobiles, typewriters, fountain pens. We never used to worry about labor differentials because our industrial techniques were such that all labor costs disadvantages were overcome. Now that foreign automobiles, typewriters, and fountain pens are knocking the stuffing out of us in the international markets and our own as well we scream bloody murder about labor costs! There was never a time in the history of this country when our businesses needed better management and greater efficiency in every area. Overwhelming foreign competition in foreign and domestic markets is no longer a threat; it is a fact.

It is obvious that we need in administration and management many more men of superior intelligence, imagination, vigor, experience, and training. But how are we going to get them when we've done everything possible to destroy native initiative? Our welfare state has promulgated the certainty of security. So kids getting out of school now are interested in pay rates, pension plans, fringe benefits, and hours of work. They are keenly interested in advancement too—meaning more pay—but disinterested in the work they have to do to earn more pay.

In this age of great and growing corporations, we have lost the proprietary attitude people once had when so many of them were founding—and owned—the companies that since have become great. Nowadays young people are indoctrinated with the idea of getting a job with a corporation that is impersonal and somehow alien to them. There must be some way of generating that sense of ownership in regard to a job which once motivated people who started their own businesses.

Another factor in leadership we have lost—of necessity because of the increasing complexity and size of our economy—is self-reliance. People who were not engineers or university men once built bridges, roads, canals, dams, railroads, and houses. In the days when this nation was being built there were no engineers at all and damned few university men. Nowadays we must have appropriate labels and wide experience before we can tackle anything. Nobody wants to trust the individual. He is bound by red tape and committees and hounded by accountants.

Nothing develops the sense of responsibility like the authority to spend the corporation's money. But no one has such authority any more. I know corporation presidents, who lack the authority to spend 50 dollars of corporate money without approval of their budget committees or finance committees. It's a hell of a state! And we can thank our accountants for it.

We look upon government employees with contempt as "bureaucrats," but the average large corporation is as bureaucratic as any government department ever was.

In my opinion, we are in more critical need of capable administrators and managers that we are of engineers and scientists, in spite of all the hullaballoo in the papers to the contrary. We need the direction of men of intelligence, integrity, vision, and guts. I am sure that the supply of such men is adequate. Our problem is to identify them, to train them, and to give them the responsibility and authority that will nurture their talents.

Words of Wisdom

The following quotation from *Barron's* of September 12th 1960 shows that thoughtful people are not inimical to the drug industry. Thank God we have a few friends!

3 ways to PRECISION LABELING

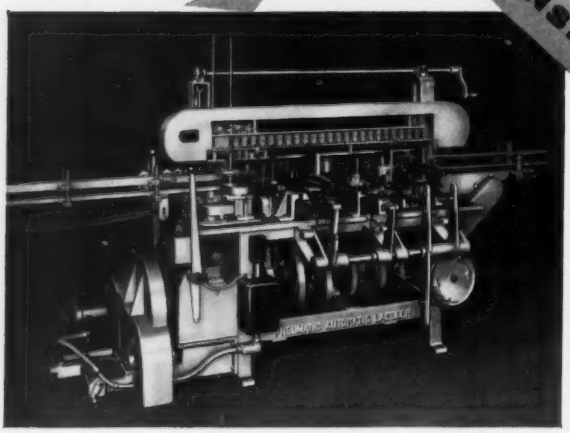
COLLETTA

McDONALD

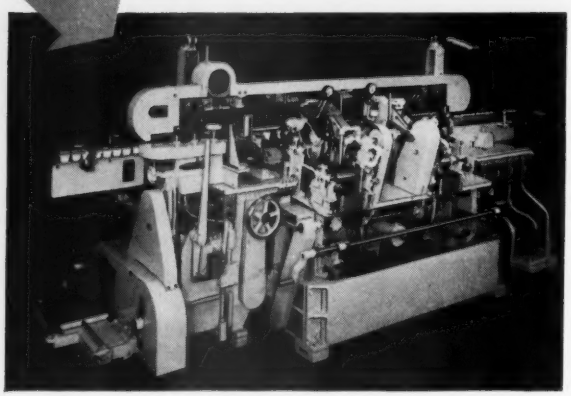
DIREC-TRANSFER

Portable bench type labeler for convenient application to wide range of shapes in glass, boxes, cartons, books and other objects. Offers full-surface gluing for high quality results. Changing from one job to another is a simple procedure, taking a maximum of five minutes.

Basically a semi-automatic unit, this model is easily made automatic by the use of available auxiliary attachments. Designed by Jagenberg of Dusseldorf, this precision built labeler is sold exclusively in the United States by Pneumatic.



This 4" Simplex unit is one of several models offered by Pneumatic as standard labeling equipment for over thirty years. Using 'glue on bottle' method for label pick-off, the McDonald Labeler has proved its efficiency in literally hundreds of installations. All models are well equipped with safety devices to prevent loss of production time and materials. Round, oval or rectangular shapes may be run with front only or both front and back labels being applied simultaneously.



Duplex in action, this Labeler handles two containers at a time for front only or both front and back application. A three-station indexing turret with suction pads picks labels off bottom of label stack as turret revolves in counter-clockwise direction. Each label receives thin, uniform coating of adhesive from roller and is given time to "temper" as it travels to next station. At final position of turret, the label is transferred directly, through contact, to bottle. Continuous straight-through intake provides gentle handling of glassware, and bottles are in positive control throughout labeling process. Equipment includes "no bottle, no label" and "no label, no glue" safeties.

PNEUMATIC SCALE CORPORATION, LTD., 70 Newport Avenue, Quincy 71, Mass. *Sales Offices: New York; Chicago; Dallas; Rochester. Agents: Fred Todt Company, Los Angeles, San Francisco and Seattle; Rockwell Pneumatic Scale Ltd., London N. W. 2, England; O. R. M. A. Paris, France. Subsidiaries: Delamere & Williams Co., Ltd., Toronto; Carbert Manufacturing Co., Inc., Cambridge, Mass.*

Packaging and Bottling Equipment

"The vast proliferation of new developments has been denounced by some as needlessly costly. The industry stoutly disagrees. In any case, what is certain is that during the past twenty years, domestic drug makers have produced more remedies for more ills than at any other time. Since 1945, the death rate from eight major diseases, including diphtheria, whooping cough and pneumonia, has been cut in half. Tranquilizers, pills for diabetes, oral polio vaccines have moved with record-breaking speed from laboratory to drug store. In the process the industry undoubtedly has made money. It also has made an unprecedented, if scantily recognized, contribution to U. S. productivity and health.

"Viewed in this light, the Kefauver investigation is not merely mischievous but also potentially harmful. For to judge by the actions of its chairman, its findings are designed to pave the way for greater federal control over the manufacture and distribution of drugs, possibly including so-called reforms in the patent and licensing laws. Such far-reaching changes, the industry has warned, easily might impede, if not destroy, its remarkable progress. Here, in truth, looms a cure that is infinitely worse than the imaginary disease. Political quackery may make headlines and, perish the thought, even national policy. It can never serve the general welfare."

Advertising Value of Factories

Recently I debated with a client the advertising value of a new plant along a main road. This chap was sore as hell when he discovered that a new main highway was to be built past his new plant. Since he could do nothing about the situation, he consoled himself with the thought that his new plant would have a lot of advertising appeal to the doctors using the main road on the way to Florida vacations. Now the guy who arrived at this conclusion is regarded as a very sharp guy in matters of merchandising and advertising. Now let's see what the advertising effect of his factory would be on the doctors of this country:

About one-tenth of one per cent of all our people are practicing doctors. We have 175,000 doctors in 175 million people. Now let's evaluate the visual effect of this factory on the doctors passing by.

Let's assume that all the doctors in the country use this road at least once throughout the year. Let's assume further that cars pass the factory at the rate of ten thousand daily. That's a lot of cars to pass any given point. Using our national averages, it is seen that ten out of the ten thousand cars would be driven by doctors. Since it is ridiculous to assume that all the doctors in the country would ever pass any given point, the reality would be that probably not more than one of the ten thousand cars would be a doctor's. And he'd probably not recognize the name of the company anyway.

The influence of the name of an ethical drug company on a factory building is exactly nil in its effect upon the lay public because the public is not familiar with the names of ethical drug companies. Even the names of many if not most of the proprietary drug and cosmetic houses are not known to the general public. Advertised product names are recognized of course and when a company plasters its product names all over the facade of its factory building as Bristol Myers does on its Hillside, N. J. factory along route 22, it utilizes its factory facade as a billboard. It's value is actually less than that of a billboord because a billboard's message can be changed frequently but the facade of a building can't.

When the traffic of heavily traveled main roads is analyzed, it will be found that a large per cent of it is constituted of workers passing to and from work. Such people may bestow a cursory indifferent glance at a new factory if it is attractive enough. But when its newness passes the habitual traveler passes the new factory without giving it a momentary glance.

I don't think a factory building should be made into a billboard. I don't think billboards should be located anywhere on the premises. They are a curse and an abomination. But I do think factories should be made as attractive as good architecture and good landscaping can make them inside and out. There are some cases when factories have been so well designed that they can be used—*if they are conveniently located*—to impress financial people, foreign customers and bands of organized tourists. I once asked the sales-manager of a company, which, for years had made a habit of lavishly entertaining medical students in its plant, what feature impressed the students most. He said. "The gin."

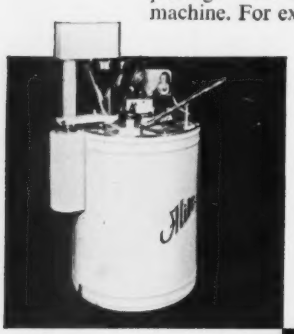
Bureaucratic R&D

It's not so many years ago that all development work was done by experienced production people. Some companies had no pilot plants at all, and research products went directly from the laboratory to the plant. Other companies that had pilot plants did not carry a new product beyond the pilot-plant stage. Production people were expected to take over then, and write their own manufacturing procedures. Now, in many plants, the R&D department assumes the whole responsibility and practical, experienced production people are not even consulted until all specifications and procedures are written and the product is ready for large-scale production. This may be all right if the pilot plant is operated by seasoned old hands who know the plant and its equipment. But I find in a lot of R&D departments a lot of smart young scientists who have had no practical experience at all. I realize, of course, that there are old timers who insist there is no proper way to make a product except the way they've always made it. But as a rule, the consistent use of the old timers' experience right from the beginning of development projects will save a lot of time and money and prevent costly blunders later on.

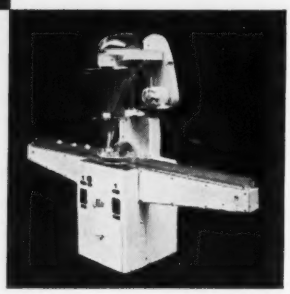
...One of the few

"containers" an **ALITE** machine doesn't fill!

But keep in mind: *"If it's pasty, powdery and pours, there's an Alite to do the pouring."* Drugs in 8-milligram vials . . . mustard in 3-pound tins . . . make-up in compacts . . . flour in 2-pound bags . . . you can put virtually any-type product into any-type package with a specially designed Alite machine. For example:



Fills up to 1200 powder compacts per hour. Arenco-Alite A. T. 5 powder-compressor is fully automatic, dispenses any powder concentration evenly, accurately. Pressure completely variable from 40 to 1000 psi with merely the turn of a knob. Handles any-size compact from 1"-4", requires no air supply or other "extras."



16, 32 or 48 fills per minute. Alite loose-filling machine speeds dispensing of powders, grain substances, even pastes, with an economical accessory. Fills containers as small as ¼ oz., as large as 3-pounds-plus. Hopper and working parts can be stripped, cleaned and reassembled in minutes.

And these are only two members of the Alite family of powder-filling, -compressing and batch-mixing equipment. For complete information, write today.

ARENCO

ARENCO MACHINE COMPANY
INCORPORATED
25 West 43rd Street, New York 36, N. Y.

Heat-Resistant Strip-Package Imprinter

Adolph Gottscho, Inc., Hillside 5, New Jersey, has introduced a variable-size imprinter for strip-packaging machines to apply trademarks and the like to heat-sealed unit packs. It uses a heat-resistant fluid ink that withstands heat sealing and will not come off on sealing rolls. The 780 Rolaprinter accommodates a wide variety of typewheels between six and 12 inches in circumference, and can print areas up to ten inches across, on webs of film, foil, and paper.

Electronic Moisture Register

An electronic moisture register, G-6, reported to provide the fastest moisture test available on many granular, ground, powdered, loose, or shredded materials, has been introduced by Moisture Register Company, P. O. Box 910, Alhambra, Calif. It requires one minute per test and no special training for use. It employs high hydraulic pressure to assure a homogeneous sample.

Air Compressors

A new line of 100-pound air compressors in the 25 to 100 h.p. range has been introduced by Clark Bros. Company, Olean, New York. These C-Line units are two-stage, air-cooled and feature compactness, durability, and high efficiency. They eliminate freeze-ups and scale formation, and operate at very conservative piston speeds to assure optimum efficiency and long life. A constant-speed load and unload device is standard; for intermittent operation, a dual control is available, which can be set for both motor and compressor, or for continuous motor operation and free air compressor unloading.

Automatic Folder

The first mass-produced machine that automatically folds small package inserts is available from Super Speed, Inc., Chicago, Illinois. The machine, the Master Minifolder, can fold hundreds of inserts per minute, each folded as many as eight times, to the thumbnail size of nine-sixteenths of an inch. Manufactured in Bielefeld, West Germany, by Herzog-Heyman, it takes a maximum sheet of 8½ by 11¾ inches, a minimum of 2 by 2¾ inches, with a minimal width fold of nine-sixteenths, has a stream-suction hopper feeder, and is lubricated centrally with a hand pump.

Automatic Container Feeder

MRM Company, Inc., 191 Berry Street, Brooklyn, New York, has designed an automatic feeder capable of handling all shapes and sizes of glass, plastic, and metal containers at speeds up to 250 per minute. It has variable-speed motor and travel control, an air cleaning device to remove lint and such foreign bodies from the container before filling, and can operate with any existing production line.

The contract packager had the answer... *another success story from the ISOTRON file.*

His "kid glove loading" insures aerosol quality

Some of the world's most pampered aerosol products start in the air-conditioned, dust-free and humidity-regulated plant of Gard Industries, Inc., a pioneer contract packager of Northfield, Ill. Controlled-quality methods from testing to loading assure consistency and stability for all types of quality aerosol packaged sprays, foams and powders.

Whatever you want to market, Gard offers years of experience, plus complete, modern facilities for research, manufacturing and marketing of aerosol products. Special environmental-controlled production lines are available for high-speed, isolated filling of quality drugs and cosmetics; paints, insecticides and other household products; and food products. A separate department is maintained for small runs on any product. If your needs involve testing, analysis, formulation or marketing assistance, Gard can serve you well.

Experienced packagers like Gard Industries know well the importance of the proper container, valve and propellent to the success of your product on the market. Increasingly often, they specify ISOTRON® . . . the extra-pure, extra-dry, factory-sealed propellents that help insure the consistent quality of your aerosol product.

ISOTRON—*The Key to Modern Living*

Pennsalt® Chemicals
ESTABLISHED 1850

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PENNSALT CHEMICALS CORPORATION
Three Penn Center
Philadelphia 2, Pa.

Perfumer's Shelf

Sandela GD

To fill the need of the perfumer for a functional product to replace sandalwood oil, Givaudan-Delawanna, Inc., offers Sandela GD. This chemical entity reproduces the characteristic, persistent and tenacious odor of the natural oil; it is available in commercial quantities at a low, stable price at present less than 1/3 the market price of sandalwood oil itself, and brings to the perfumer an exceptional product with which he can replace one of his natural tools.

Sandela GD is a clear, colorless liquid with the characteristic odor of sandalwood. Its specific gravity at 25°, compared with water at the same temperature, is 0.965-0.975 and its refractive index at 20° is 1.4900-1.4990. The acid value of the compound is 5, and saponification value 30 to 40. It is clearly soluble in two volumes of 80 per cent alcohol and miscible with 95 per cent alcohol. It is insoluble in glycerine and water but very soluble in diethyl phthalate, benzyl benzoate, isopropyl myristate, corn oil, soya oil, mineral oil, dipropylene glycol, benzene, hexane, and carbon tetrachloride.

This new material can be used in perfume formulations in exactly the same manner as sandalwood oil. In perfume compositions, it gives the same persistent basic characteristics, making it suitable as a direct ounce-for-ounce replacement of the natural oil. In blends, it exhibits excellent residual properties considered to be far superior to those of sandalwood oil.

Sandela GD, sandalwood oil, and santalol were exposed on blotters for a period of three months and examined periodically. Sandela GD loses none of its odor intensity and character and it retains its persistence and stability for a longer time than sandalwood oil and santalol.

Sandela GD, utilized in place of sandalwood oil, gave perfume extracts, colognes and toilet waters which showed remarkable trueness to compounds containing natural sandalwood oil.

With this new substance which is readily available and extremely economical when compared to sandalwood oil, the perfumer can obtain the desirable long-lasting, distinctive woody notes so popular in modern fragrances. He need no longer be restricted to the low concentrations dictated by the high price and limited availability of sandalwood oil.

Cakes of soap containing 0.5 per cent and 1 per cent of Sandela GD were shelf-tested over an extended period of time. Some cakes were left exposed to daylight and air. Although on initial examination, slight differences between soaps containing Sandela GD and cakes containing sandalwood oil, may be detectable, after many months, the odor of the new substance is still strong and persistent without loss of any of its original character, while sandalwood oil has lost most of its initial odor.

In perfume compounds for soap, Sandela GD has proved itself an outstanding replacement for sandalwood oil. Soap compounds were prepared containing varying concentrations of Sandela GD and were compared with identical blends containing the same concentrations of sandalwood oil. Upon examination both on the blotter and in soap cakes, it was found that the blends were identical.

Tests were also conducted with powdered soaps using a concentration of 0.5 per cent of Sandela GD. The aromatic remained unaffected by oxidation or evaporation, giving exceedingly persistent perfuming effects superior to those obtained with sandalwood oil. In the powdered soap, Sandela GD proved to be far more stable than sandalwood oil.

Sandela GD was evaluated in typical liquid and powdered detergents, including heavy duty types, at a concentration of 0.5 per cent. The test samples were subjected to elevated temperatures (110° C.) for a period of seven days. Examination revealed that the perfume was not adversely affected even at pH 11, its odor remaining stable and unchanged.

In a cosmetic lotion, a vanishing cream, and a deodorant cream at a concentration of 0.5 per cent, Sandela GD revealed excellent retention of its sandalwod character and no visible signs of change in the color and consistency of the cosmetic base.

A talcum powder was prepared containing 0.1 per cent of Sandela GD and test samples were examined periodically for signs of oxidation or rapid evaporation. Results indicated that the odor remained stable and unchanged in its sandalwood character.

A thorough examination of Sandela GD in pressurized products was conducted. The usual evaluation of solubility, stability in the various propellants, corrosion and clogging tendencies, odor change, etc. indicated that aromatic would present no difficulties in this packaging medium.

It was also found to be completely suitable for products to be packaged in polyethylene because of its extremely low permeation rate and its stability to air.

Eau de Cologne Oils

The principal ingredients of the eau de Cologne originally devised were citrus fruit oils and, first among these, oil of bergamot according to F. La Face (*S.P.C.* 33: 952, 1960).

Special properties are associated

with the complex constitution of the oil and linalyl acetate and linalol are accompanied by various substances, which have an important part to play in the formation of the "bouquet." The many investigations have in fact revealed that in the alcohols group, besides linalol, dihydrocuminol, nerol, geraniol and terpineol are present. In the class of esters, linalyl acetate is accompanied by the acetates of geranyl, neryl, terpinyl; among the carbonyl compounds, together with citral, we find three higher fatty aldehydes; in the non-volatile fraction, which also is of importance, products of a coumarin nature have been discovered.

This complex constitution of the odoriferous group in oil of bergamot (which does not rule out the possibility of further substances, as yet unknown, being present) accounts for its particular characteristics and makes it possible to appreciate why all attempts so far made to reproduce the original tone and replace its effects have been vain.

The traditional formula of eau de Cologne makes use of essential oils of lemon (*Citrus limonum*) and sweet orange (*Citrus sinensis*). For these citrus fruits the characteristics of the peel, which is the seat of the oil, are not the same as in the case of the bergamot.

So far as the olfactory note of lemon oil is concerned, it should be remembered that the characteristic content of citral is present with other substances that explain the considerable difference in effects and uses which it displays by comparison with different essential oils which are very much richer in citral. Indeed, apart from the fact that in lemon, besides α and β citral there is also found γ or isocitral, to which is attributed a softer and finer note than the other two forms, the constitution of oil of lemon includes various other constituents belonging to different oxygenated groups—alcohols, aldehydes, esters.

Of interest, too, is the essential oil of sweet orange. For this citrus fruit the same programme and the same techniques apply as are given for lemon.

In sweet orange oil the basic note is furnished by decyl aldehyde, which, however, is accompanied by other higher fatty aldehydes, free and esterified alcohols which make up, modify and round off the principal note, providing a fresh and penetrating fragrance.

The contribution of the citrus fruits to the classical formulas of eau de Cologne is completed by two essential oils distilled from the blossom and leaves of the bitter orange, *Citrus bigaradia*, Risso.

Oil of neroli provides one of the essential notes of eau de Cologne. The essential oil contains nerol, geraniol, phenylethyl alcohol with its rose note, indole and jasmone (which are common to jasmin), farnesol and nerolidol (among the components of acacia), free linalol and, its acetic ester, methyl anthranilate and others.

The harmonious blending of all these odors gives rise to a gentle flowery note which is the indispensable basis of good eaux de Cologne and enters into the formulas of a large number of high-class compositions.

Together with flower oils, bitter orange also furnishes petitgrain, a distillate from the foliage. Various components are common to both petitgrain and oil of neroli, although in some cases the contents vary appreciably; in fact, linalyl acetate is present in petitgrain up to 6-8 times the extent to what is found in neroli, while the latter essential oil is richer in free linalol. Besides these substances, however, which together amount to 85 per cent of the essential oil and more than 90 per cent of the oxygenated substances, there are the alcohols geraniol, terpineol, nerol and their acetic esters, while the fluorescence is to be attributed to methyl anthranilate.

In the eaux de Cologne of the classical type, invented at the beginning of the seventeenth century, the citrus fruit notes, in conjunction with those of some Labiates, including lavender as the most important, rosemary and balm to a lesser extent, and clary sage at a later date, all make a useful addition to the preparation.

The composition of the French and Italian oils is very similar from the qualitative point of view and also because they have for main constituents linalol and linalyl acetate, which together exceed 75 per cent of the oil. There are also other components, less important as regards quantity, but decisive for the formation of the "bouquet." As regards esters, besides linalyl acetate, which nevertheless represents 95 per cent, the essential oil also contains butyrates, caproates of linalol, borneol and lavandulol, alcohols which are also found in the free state.

In the lavender oils there are likewise small quantities of nerol, cineol, coumarin and a ketone, ethyl-n-amyl ketone, which has a fresh characteristic odor and plays a large part in determining the fragrance.

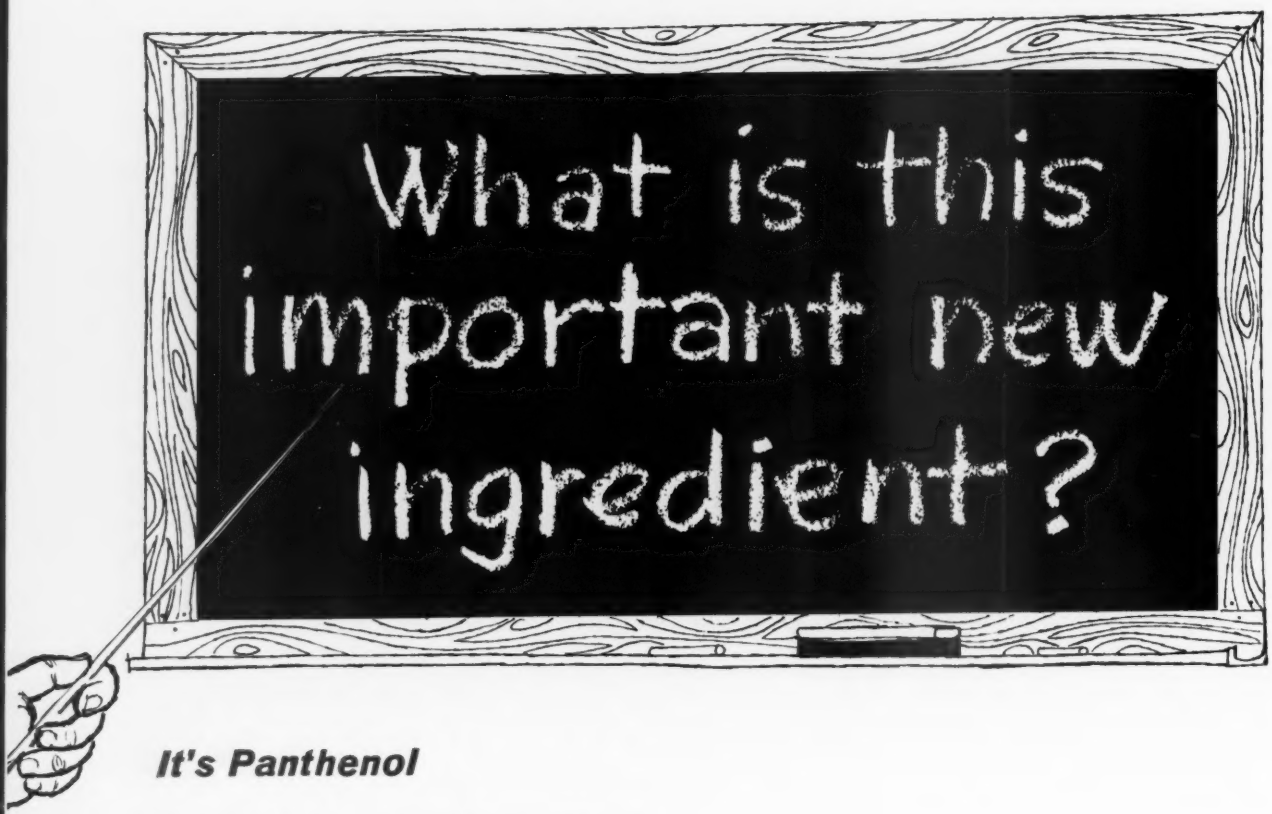
Of the other species mentioned in the original formulas of eau de Cologne, rosemary—*Rosmarinus officinalis*—was used of old in medicinal preparations and even in toilet waters, the most popular of which was Queen of Hungary water.

The note of oil of rosemary is the outcome of the olfactory blending of borneol, which is found in the free state, and as acetate, cineole and camphor.

Essential oil of balm, distilled from the fresh plant of *Melissa officinalis* collected at the beginning of flowering, is better known for its sedative and anti-spasmodic action, but it also has merits as an odorant through the tempered lemony note made up by the presence, together with citral, of citronellal and certain alcohols, among which the following have been identified: citronellol, geraniol and linalol, besides a variable quantity of esters.

One essential oil which, although not appearing in the ancient formulas of eau de Cologne, has nevertheless been employed in compositions of the classical type, is that which is obtained from *Salvia sclarea*.

Among the components of this essential oil, which is produced largely in the USSR, but also to some extent in France, Italy and Hungary, linalyl acetate plays the greatest part, attaining up to 70 per cent; it is accompanied by free linalol, nerolidol and its acetic ester, other alcohols such as nerol, geraniol, terpineol and sclareol, as well as by a fraction of marked musky character which yet remains to be identified. From the combination of these constituents is produced a characteristic odor that is manifest in a pleasing head note and a slightly musky tone, which slows down the volatility of the finished product, without altering unduly the persistence characteristics.



It's Panthenol

Here are fast facts about **PANTHENOL:**

Just what is **PANTHENOL***?*

PANTHENOL is the alcohol of pantothenic acid, an important member of the vitamin B-complex.

What will **PANTHENOL** *do in my formulas?*

PANTHENOL helps to soothe and heal chapped, rough skin; promotes normal growth of skin and mucous membranes; helps groom and keep hair healthy, lustrous, and attractive.

Is **PANTHENOL** *safe?*

Yes. Dermatologists and other members of the medical profession have prescribed PANTHENOL for years. They have administered PANTHENOL topically, orally, and by injection. Numerous reports published in medical journals confirm the safety and usefulness of PANTHENOL.

What other advantages?

All these: PANTHENOL is stainless, water-washable, harmless to lips, skin and hair. It's stable, and can be combined with other vitamins, such as A, B_6, D and E.

Who makes **PANTHENOL***?*

PANTHENOL is made by Hoffmann-La Roche Inc., a pioneer in the synthesis, development and large-scale production of many of the most important vitamins.

Tell me a few uses for **PANTHENOL.**

You'll find PANTHENOL particularly valuable in cosmetic and toilet goods formulas, such as:

Lipsticks	Hand Lotions	Hair Tonics
Face Creams	After-shave Lotions	Deodorants
Body Creams	Hair Sprays	Anti-Perspirants

Can I use **PANTHENOL** *with my present equipment?*

You can incorporate PANTHENOL into your formula with your standard equipment.

Where do I get complete information about **PANTHENOL***?*

From Roche! Get free informative, helpful literature by contacting your local Roche representative. Or send your inquiries directly to the Roche Technical Service Department. Send today.

Available on request—"Panthenol in Cosmetics", by S. H. Rubin, L. Magid, and J. Scheiner, reprinted from Proceedings of the Scientific Section of The Toilet Goods Association, Number 32, December, 1959.

Vitamins Come Right from Roche

Round the World

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In Canada: Hoffmann-La Roche Limited, Vitamin Place, 1956 Bourdon Street, St. Laurent, Montreal 9, Quebec

Compounder's Corner

Embryo Hydrolysates in Cosmetics

"The importance of using amines in cosmetics and the now proved stimulant effect of embryonic extracts in the therapeutic and cosmetic field gave us the idea to proceed with our researches, associating in one single product the constructive value of the different amino acids deriving from the enzymatic decomposition of the protein tissues of an embryo and the vitalizing power of the trace elements present in the embryo, which catalyze and influence the processes of reproduction and regeneration of the cells." With these assertions, V. Lodi and P. Rovesti reported to the XIII International Congress of Cosmetics in Lucerne, according to "*Perfumery & Essential Oil Record*, vol. 51, p. 496, a preparation made by the trypsin hydrolysis of normal bovine embryo. Chromatography showed the following amino acids: arginine, histidine, lysine, tyrosine, tryptophane, phenylalanine, cysteine, methionine, threonine, serine, leucine, isoleucine, valine, glutamic acid, aspartic acid, glycine and alanine. The hydrolyzate was used as a wet compress of a 5 per cent solution or as 2.5 per cent in a bentonite gel for oily skins or 2.5 per cent in a lanolin cream for dry skins. The "active" product was applied to the right side of the face, the blank to the left side, six subjects with the compress, six each with the two creams. For the wet treatment, "the result was satisfactory, both on the acne of the very young women and the wrinkled and withered skin of the older women." Oily skins showed the following signs of improvement, according to the authors: "tightening-up of the pores, attenuation of scars or spots left by acne ailments, clearing of sallow and pale look."

"At the end of the treatment this improvement was clearly visible on the right side of the face, which had a healthier and more homogeneous look, resulting obviously from the nourishment of the skin."

For sensitive and dry skins, "the most salient results were improvement, and in some cases, complete disappearance of the small wrinkles around the eyes and the mouth, disappearance of the sallow look and spots, a more transparent and firmer skin due to a healthier elasticity of the muscles."

Lodi and Rovesti then conclude that the favorable results can be interpreted as "a sign of stabilization of a balanced metabolism of the cells and also of an increase of vital energy and of renewed activity of the germinative stratum."

Comment: The five references appended to the article are by the same authors and refer to reports given at various International Aesthetics and Cosmetics Congresses, as if the work had not been presented to publications with scientific standing. Most certainly, work of this nature would get short shrift from the Federal Trade Commission and the Food and Drug Administration in the United States.

New York S.C.C. Meeting

At the first fall meeting of the N. Y. Chapter of the S.C.C., Dr. W. C. Hueper of the National Cancer Institute energetically defended the inclusion of the Delaney Cancer Clause in the Food Additives Amendment and the new color additives bill. Dr. Hueper's paper, "Potential Cancer Hazards from Cosmetics to Producers and Consumers" was presented before 120 members of the SCC at the Sept. 7, 1960 meeting at the Hotel George Washington in New York City and evoked a lively question and answer period.

A carcinogen can be defined as a material which does not merely produce a significant increase in cancer, but one "characterized by being capable of producing in animals, including man, cancers which would not occur without the intervention of these agents."

Even materials causing benign tumors in experimental animals should be suspect, because most carcinogens can be made to elicit benign as well as cancerous tumors in some experimental animal or other. Toxicity of a compound is totally unrelated to carcinogenicity and cannot be taken as a measure of cancerous potential.

"The only safe dose of an actual or potential human carcinogen is a zero dose," Dr. Hueper declared, and he further feels that it is impossible to establish levels for limited amounts of carcinogenic additives. The scatter pattern of cancer among members of the general population and the relatively low general cancer attack rates for different organs indicates, according to Dr. Hueper, that the great majority of carcinogenic influences acting upon the population must be of rather weak nature. Crude and semi-refined paraffins and paraffin oils have been observed to cause cancer. Dr. Hueper recommends that strict control over the type of crude oils, method of processing and of refining might be wise, and that quality control of materials intended for cosmetic purposes be tightened to include bioassays in animals.

Carbon blacks, wood tar, and wood creosite may contain carcinogenic chemicals and Dr. Hueper feels there is no place in cosmetics for these products. Carbon blacks free from tarry admixtures are available and should be used.

Because they sometimes contain traces of beta-naphthylamine, Yellow OB and Yellow AB should be prohibited, even for external use. They are no longer used in cosmetic preparations. Dr. Hueper concluded his presentation by saying that, "We must learn to live sensibly with the many new and largely untested chemicals which are introduced in an unending stream into the human environment and to which mankind has not had an opportunity to become biologically adapted."

(*Continued from page 474*)

size in contrast to penicillin G and phenethicillin.

Studies on the bactericidal activity of the penicillin have shown that it is equally as bactericidal to a penicillin G-resistant staphylococcus strain as it is to a sensitive one.

In animal protection tests, using *Diplococcus pneumoniae*, *Streptococcus pyogenes*, and a sensitive *Staphylococcus aureus*, the new penicillin was able to cure overwhelming infections when administered intramuscularly. The dose required, however, against these penicillin G-sensitive organisms was larger than that with penicillin G. In the case of animal protection tests using resistant *Staphylococcus aureus* strains, extremely high doses of penicillin G were not able to cure these infections. However, infections were readily cured by penicillin x-1497.

Penicillin x-1497, 6-aminopenicillanic acid (6-APA) and penicillin G were compared by *H. G. Steinman* as substrates for cell-free preparations of penicillinase obtained from *Bacillus cereus* and from *Staphylococcus aureus*. Penicillin x-1497 was hydrolyzed by penicillinase at a very low rate compared to the rate for penicillin G, the rate for 6-APA being intermediate. The rates of hydrolysis of penicillin x-1497 and of 6-APA by the enzyme from *B. cereus* were three-fold greater, relative to penicillin G, than by the enzyme from *S. aureus*.

The two new penicillins were also compared with penicillin G with respect to the rate with which resistant mutants could be selected by means of subculture in increasing concentrations of the antibiotics. A staphylococcus was obtained by this procedure whose resistance to penicillin x-1497 increased exponentially through six successive subcultures. This resistance was not a function of penicillinase content or of altered penicillinase reactivity, but rather resembled the penicillin resistance obtained with nonpenicillinase producing strains of staphylococcus.

In vitro sensitivities were performed by *S. M. Finegold et al.* with penicillin x-1497 and a variety of aerobic and anaerobic bacteria and, for the most part, the bacteria were resistant.

Ninety-nine strains of coagulase-positive *S. aureus* isolated from clinical material were tested with a tube dilution technique.

All were sensitive to x-1497, while some resisted penicillin G. The 99 staphylococci tested represented a wide variety of phage types and a number were resistant to the following antibiotics: streptomycin, tetracycline, chloramphenicol, bacitracin, erythromycin, novobiocin, kanamycin, neomycin, and paromomycin.

Twenty-two strains of anaerobes (including clostridia, microaerophilic and anaerobic streptococci, *Lactobacillaceae*, *Actinomyces bovis*, *Bacteroides*, and fusiformis) were studied for sensitivity to penicillin x-1497, penicillin G, and phenethicillin using a plate dilution technique. Most strains were quite sensitive to pencillin G and virtually as sensitive to phenethicillin. Penicillin x-1497 was distinctly less active against a number of these strains.

The performance under identical conditions of three penicillins, penicillin G, phenethicillin, and penicillin x-1497, was studied by *L. J. Griffith et al.* *Staphylococcus aureus* var. pyogenes ATCC 6538P was used to test this performance. It was found that penicillin G produced the greatest amount of growth inhibition, followed by phenethicillin and penicillin x-1497. Doubling the concentration of antibiotics in the discs produces very slight change in the amount of inhibition on the test organism.

Penicillin discs made from rigidly controlled dilutions of the three penicillins were used to calculate the antibiotic survival time under seven storage conditions. Penicillin G proved to be the most stable, followed by phenethicillin and penicillin x-1497. Data seem to indicate that penicillin x-1497 was inactivated rapidly at room temperature and 37° C.

Fifty-seven strains of staphylococci, isolated from clinical sources, were tested by *K. Casson and J. Lannon* for sensitivity to penicillin x-1497 by the two-fold tube-dilution technique and the disc method. The minimal inhibitory concentrations, with one exception, were within a range of 1.56 mcg./ml. to 6.25 mcg./ml., with the majority (79 per cent) at 3.12 mcg./ml. One culture was resistant to 50 mcg./ml. All but one of the strains tested by the disc method showed zones of inhibition.

Penicillin x-1497 was investigated pharmacologically and toxicologically in laboratory animals by *M. H. Pindell, D. E. Tisch, and J. Reiffenstein.* The material was practically devoid of irritant liability, being less painful than penicillin G when compared by quantitative tests. No cardiovascular or autonomic effects were demonstrable in anesthetized dogs. The material was poorly absorbed from the gastrointestinal tract of dogs but was readily and rapidly absorbed following intramuscular administration in both dogs and rabbits. Excretion studies demonstrated that about 40 per cent of an intramuscularly administered dose was eliminated by the kidneys within 24 hours and that four-fifths of this amount was excreted within the first three hours. Tissue distribution studies in rats demonstrated that peak tissue concentrations were attained within 15 to 30 minutes, followed by gradual diminution over the next several hours. Penicillin x-1497 showed slightly less affinity for serum proteins than did penicillin G in both dog and human serum.

Intravenous administration of 300 mg./kg. produced serum concentrations in dogs averaging 573 mcg./ml. 30 minutes after administration, diminishing to 6.3 mcg./ml. three hours after injection. The intravenous LD_{50} in mice was 3891 mg./kg., and 1297 mg./kg. was administered by this route to dogs without toxic effect. Dogs also tolerated daily intramuscu-

(*Continued on page 567*)

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(*Continued from page 459*)

pleased. After all, much effort, time, and money is constantly spent to deodorize an increasing number of consumers' goods—rubber articles, artificial leather, plastics, and the like. It has been shown time and again that among competitive products the one with the better odor sells best. We can observe the same trend in the pharmaceutical trade, as far as oral preparations are concerned. When they are made more palatable, through the judicious use of flavors, their public acceptance is increased. Dr. Donald Powers of Warner-Lambert once mentioned a panel test he and his associates made, in which the subjects were presented with two fragrances in an identical shampoo formula. The shampoo preferred by the panel was felt to give better performance than the other; in this case, better odor was unconsciously linked with quality.

If better odors increase consumer acceptance generally, why should it be otherwise in cosmetic and dermatological preparations? Why should we assume that the public will be satisfied with disagreeable-smelling preparations when pleasanter ones can be made? This does not stand to reason.

The other argument against using better ingredients is that, as a rule, refined raw materials are more expensive and, if an inferior raw material seems to give satisfaction, it is not good business practice to increase unnecessarily the basic cost of the formula.

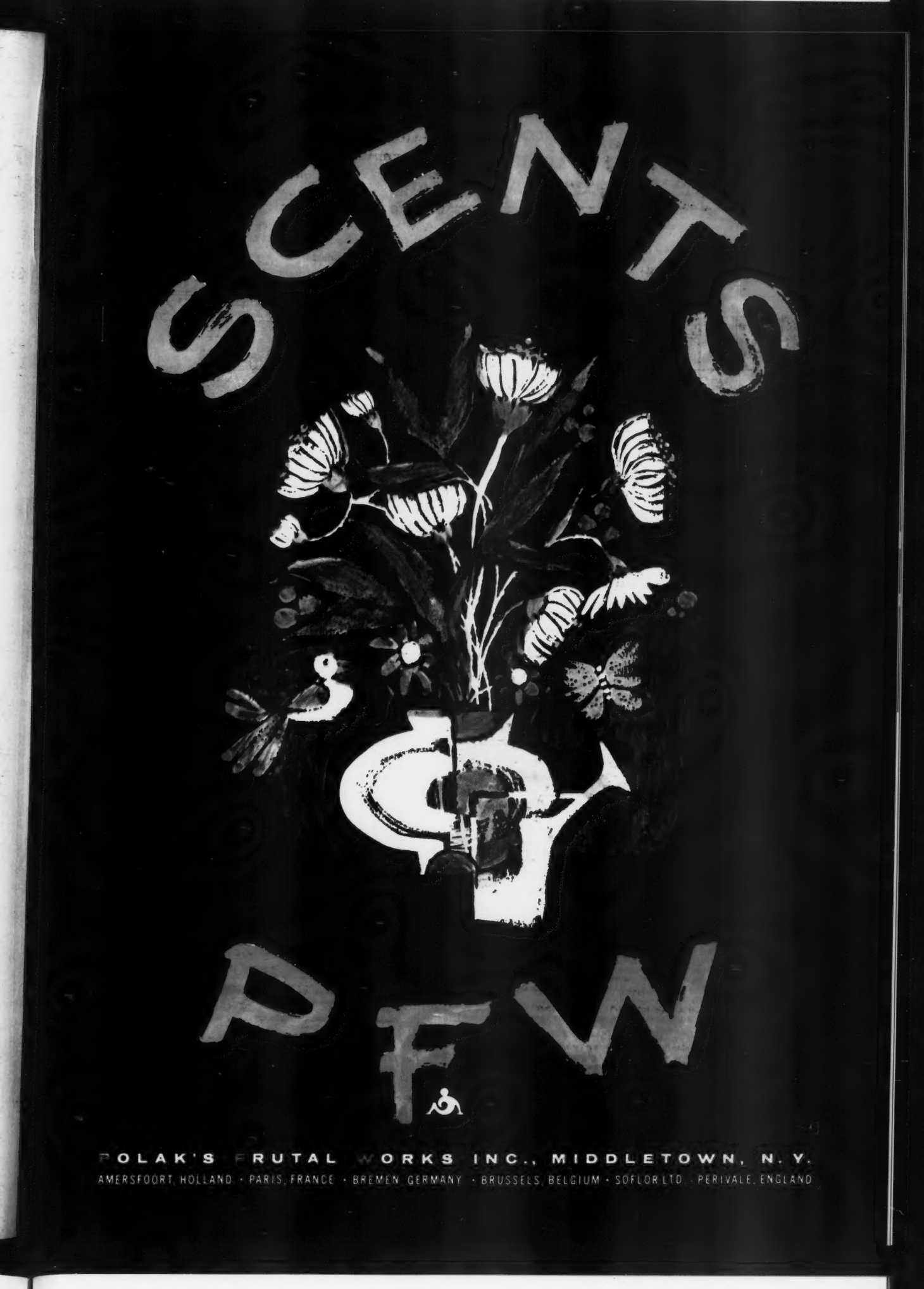
It seems to me that the argument is not well taken. It can be shown in most instances that the slight increase in cost of purified raw materials is more than offset by its enabling the formulator to prepare products with longer shelf life, and improved appearance and odor.

I once wrote on the importance of using the purest grade of stearic acid in the preparation of stearates for face powders. (Ed., Sagarin, *Cosmetics Science and Technology*, 1957, p. 227.) To paraphrase my conclusion there, it has always been our experience that it is economically sound to spend more money to acquire the best available grades of raw materials, since the extra cost is more often than not recouped easily by the savings on the amount of perfume needed and on the better quality of the finished product.

This holds true for all types of raw materials. Take lanolin, for instance. It can easily be shown by comparing an ordinary grade of U.S.P. lanolin with a refined grade having very little odor, at a price differential of four cents per pound.

Prepare solutions of both lanolins at 10 and 25 per cent in mineral oil. A great difference is noticeable in the character and strength of the respective odors of the solutions. Now, take a perfume especially developed for lanolin products, and use the minimum necessary to just cover the odor of the solutions of high-grade lanolin. Then use twice this amount in the solutions of U.S.P. lanolin. You will

(*Continued on page 542*)



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Laboratory Data Sheet

VITAMIN C

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ASCORBIC ACID, U.S.P. Roche

TYPES	DESCRIPTION AND USES
GRANULAR TYPE 20-60	100% (±) passes through 20 mesh. 95% is retained on 60 mesh. Similar to granulated sugar in particle size. Satisfactory for direct addition to dried granulations.
FINE GRANULAR TYPE 40-80	100% (±) passes through 40 mesh. 95% is retained on 80 mesh. A free-flowing product similar to table salt in particle size. Recommended for tablet granulations where fine powder is considered less suitable because of denser packing.
SUPERFINE GRANULAR TYPE 60-100	100% (±) passes through 60 mesh. Approximately 25% remains on 100 mesh. 45-50% passes through 100 mesh and remains on 200 mesh. 25-35% passes through 200 mesh. A very fine free-flowing crystal suitable for dry gelatin capsules or tableting. Useful in dry mixtures, food supplements.
FINE POWDER TYPE 100	100% (±) passes through 100 mesh. Produced by grinding crystalline material. Non-abrasive on tableting dies. Widely used for granulations, solutions, food supplements. Minimizes fractionation of particles in dry mixtures.
ULTRA FINE (MICRO) POWDER TYPE 325	Minimum 99% through 100 mesh. Minimum 90% through 200 mesh. Milled extremely fine. Practically devoid of abrasive action on cutting dies. Screen tests above 200 mesh are unreliable because of variations in technique, equipment, humidity, static charges, etc. Sedimentation tests and measurement of particle size in microns reveal that 60-70% of Roche material is smaller than 44 microns (equivalent to 325 mesh).
AMPUL TYPE	Very fine crystals—easily dissolved. Minimum color. Specially produced and tested for use in parenteral solutions. See Roche technical brochure "Notes on Vitamin B_1 and Vitamin C Parenteral Solutions" for complete details.
TYPE F	Especially produced for use in the food industry. Free-flowing, will not dust or clump, dissolves easily. U.S.P. in quality. 100% through 50 mesh. 98-99% remains on 200 mesh.

COATED ASCORBIC ACID — 97.5% Roche

DESCRIPTION

Coated ascorbic acid 97.5% Roche is a fine, white, or nearly white powder. It is pure U.S.P. ascorbic acid powder coated with ethyl cellulose. The manufacture of coated ascorbic acid is licensed under Patent No. 2,410,417 to Roche and customers of Roche.

SPECIFICATIONS

Particle Size	100% through 16 mesh screen 75-92% through 40 mesh screen 45-80% through 60 mesh screen 35-60% through 100 mesh screen
Assay	Minimum 97.5% ascorbic acid
Identity test	Positive for ascorbic acid
Loss on drying	Negligible

USES AND DATA

Ethyl cellulose coated ascorbic acid Roche has these advantages in pharmaceutical tablet manufacture:

- Small size, high potency (250-500 milligrams) tablets of light color can be made from dry granulations with very little excipient.
- Aids in eliminating chipping and capping during compression.
- Retards discoloration, mottling during abnormal storage conditions.
- Reduces contact of ascorbic acid with reactive materials.
- Rapidly available in aqueous solution for assay.
- Provides a tablet with slower release of ascorbic acid, tending to reduce localized acidity sometimes experienced with high potency tablets.

FOOD MANUFACTURERS

- Manufacturers of cured meats can use this type to advantage for retarding smokehouse activity, and for better protection in spice mixtures. It may also provide longer protection of color and flavor during storage and display.

DATA ON PARTICLE FINENESS

Based on U.S.P. XV-pages 934-5; N.F. 10, pages 702-3; ⊕Langes Handbook of Chemistry 9th Edition, page 911

The fineness of "powders" is described in both the U.S. Pharmacopeia and National Formulary in terms which are related to the number assigned to a standard sieve made of woven wire cloth. The size of wire, and sieve opening are standardized together with permissible variation in both average and maximum openings.

Sieve Number	Sieve Opening in Microns	Sieve Opening Mm.	Permissible Variation in Average Opening Per Cent	Permissible Variation in Maximum Opening Per Cent	Wire Diameter Mm.
50	297	0.297	± 5	± 25	0.170-0.253
100	149	0.149	± 6	± 40	0.096-0.125
200	74	0.074	± 7	± 60	0.043-0.061
⊕325	44	0.044	± 5	± 60	0.036

Standards are established for defining the fineness of powdered chemicals, together with a technique for determining the uniformity of fineness. The types of powders described in the U.S. Pharmacopeia and National Formulary do not represent the full range of particle sizes commercially available. No procedure is given for the determination of particle size in the "ultra-fine" or "micro powder" range, sometimes referred to as No. 325. This requires a sedimentation method and measurement in microns. Ordinary sieving methods are inaccurate.

The variation possible in the standard sieves plus such variables as the motion applied to the screen and physical characteristics of the powder being screened affect accuracy and duplicability of screening tests. Particle size specifications based on mesh sizes must always be regarded as nominal rather than as strictly accurate limits of particle size and distribution.

SODIUM ASCORBATE** Roche

This is the sodium salt of ascorbic acid. It is available as an odorless, tasteless, anhydrous, fine white powder or fine granular substance.

The antiscorbutic activity is in molecular proportion to ascorbic acid, one milligram of the sodium salt being equivalent to 0.889 milligram of the acid, or one milligram of the acid equivalent to 1.124 milligrams of sodium ascorbate.

Highly soluble in water—62 grams/100 ml at 25°C, 78 grams 100 ml at 75°C. Aqueous solutions are unstabile, easily oxidized on exposure to air, or other factors which affect ascorbic acid.

The pH of a sodium ascorbate solution is from 5.6 to 7.+ as compared with a pure ascorbic acid solution at pH 2.3-2.5. The more neutral characteristic of the sodium salt recommends it for high dosage oral forms where gastric sensitivity to lower pH might be undesirable. It is useful in combination with ingredients which would react unfavorably under more acid conditions. Products can be buffered to a suitable pH by combining sodium ascorbate and ascorbic acid together.

Commercial forms of sodium ascorbate are not recommended for preparation of parenteral solutions. It is more satisfactory to prepare suitably buffered solutions of Roche ampul type ascorbic acid, using sodium bicarbonate according to the special Roche method described in our technical brochure, "Notes on Vitamin B_1 and Vitamin C Parenteral Solutions."

Sodium ascorbate is of value as an antioxidant for use in comminuted meats and in curing pickles for hams, bacon, and corned beef. Because it is the salt of ascorbic acid (vitamin C), a substance naturally occurring in meats and identified in the U.S. Pharmacopeia, it may be preferred to antioxidants in the "chemical additive" class.

ERYTHORBIC ACID and SODIUM ERYTHORBATE

For Antioxidant Use Only — No Nutritional Claim Can Be Made — Literature on Request

****Sodium erythorbate Roche** (formerly sodium d-isoascorbate), antioxidant with virtually no vitamin C activity. A white, free-flowing crystalline material. Slightly less soluble than ascorbic compounds. When replacing ascorbic acid, 23% more should be used to obtain equal antioxidant activity and 8% more when replacing sodium ascorbate. These differences are due to the presence of both water of crystallization and sodium which are inactive.

Erythorbic acid Roche (formerly d-isoascorbic acid) — antioxidant. Similar to sodium erythorbate described above. Useful where acid reaction or absence of sodium is desirable. For equivalent antioxidant activity use 23% less than with sodium erythorbate, or the same amount as with ascorbic acid (vitamin C).

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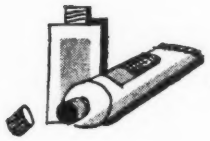


Advancing Therapy

Griseofulvin Synthesis

Two recent papers describing synthesis of griseofulvin have been called to my attention by my friend Dr. Richard H. Barry of Schering Corporation. Different approaches to the problem are used by the respective investigational groups and at least one method (depending on the economics involved in producing the natural product) offers promise of commercial synthesis. Even more intriguing is the specific statement by the Hoffmann-La Roche investigators that "other derivatives of griseofulvin can also be synthesized by the method described. Details of this work and results of chemotherapeutic testing will be published later."

A. C. Day, J. Nabney, and A. I. Scott (*Proc. Chem. Soc.* 1960, 284) of the University of Glasgow synthesized the antibiotic from a benzophenone derivative, 2-hydroxy-3-chloro-4,6-dimethoxy-2′-methyl-4′-hydroxy-6′-methoxybenzophenone which was made from 2-methoxy-4-methoxycarbonyl-6-methylbenzoyl chloride, 2-chloro-3,5-dimethoxyphenol and aluminum chloride in nitrobenzene at room temperature. This benzophenone with alkaline ferricyanide gave racemic dehydrogriseofulvin in 60 per cent yield. Hydrogenation of the latter with a special catalyst gave a mixture of 70 per cent of the original benzophenone, 10 per cent of the original dehydrogriseofulvin, 10 per cent of stereoisomers of the starting material, and 8 per cent of racemic griseofulvin. The racemic compound was resolved by acid hydrolysis to griseofulvic acid and conversion to the quinine methosalt, which was identical with the same salt obtained from the natural compound. Optically active griseofulvic acid could be regenerated from the salt, and the acid had previously been reconverted into optically active griseofulvin.

A Brossi, M. Baumann, M. Gerecke, and E. Kyburz of F. Hoffmann-La Roche & Co. A.G., Basel reported on the total synthesis of griseofulvin in a preliminary communication to *Helvetica chimica Acta*, 43: 1444, 1960. Condensation of the methyl ester of 2-hydroxy-3-chloro-4,6-dimethoxybenzoic acid with methyl bromoacetic acid gave the oxyacetate ester which was condensed to 4,6-dimethoxy-7-chlorocoumaran-3-one-2-carboxylic acid methyl ester. Condensation with 3-pentene-2-one gave a mixture of stereisomeric racemates which were separated by fractional crystallization. One of these when treated with sodium methylate gave the desired spirocyclic ketone, racemic epi-griseofulvinic acid. Treatment of the last compound with diazomethane gave an enol-ether mixture of the racemates of epi-griseofulvin and epi-isogriseofulvin which were separated by chromatographic treatment. Racemic epi-griseofulvin was partially isomerized by means of sodium methylate and racemic griseofulvin separated. The racemic antibiotic was resolved by isomerization to the iso-griseofulvin which was saponified to griseofulvic acid. The brucine salt was used for resolution and the active salt converted to the optically active griseofulvin, identical in every respect with the natural product.

Oral Drug Absorption

Studies in normal animals have contributed little to our understanding of the mechanism of drug absorption, mainly because of the inherent physiological variables and the difficulty in making quantitative estimates of the rate of absorption, according to L. S. Schanker in a review in *Journ. Med. Pharm. Chem.* 2: 343, 1960. Although the normal animal is extremely important in the final appraisal of the absorption of a given compound, it is only when most of the physiological variables are eliminated and drugs are administered in true solution that the scientist clearly sees the two physical properties of drugs which are important in determining the rate of absorption: (1) the lipid water partition ratio of the undissociated drug form; and (2) the dissociation constant, which determines the proportion of drug in this form. Thus weak organic acids and bases are readily absorbed when present as the lipid-soluble, uncharged molecule. Completely ionized drugs like the quaternary ammonium compounds and sulfonic acids are absorbed with great difficulty. Un-ionized substances with very low lipid-solubilities like sulphaguanidine are absorbed slowly. This may be explained on the assumption that the barrier between the gastrointestinal tract and the bloodstream behaves towards foreign compounds as a lipoid membrane.

With this information, the medicinal chemist is at last in a position to make predictions concerning the gastrointestinal absorption of drugs on the basis of known physico-chemical properties.

Other factors may modify absorption. For example, some drugs appear to be poorly absorbed, but actually are unstable in the gastrointestinal tract. Other compounds, especially acidic drugs, are absorbed slowly because they precipitate in the fluids of the stomach and intestine; their rate of solution now becomes the factor limiting the rate of absorption.

Numerous studies have shown that drugs are absorbed more slowly from suspensions or from solid dosage forms than from aqueous solutions. Advantage has been taken of this principle to prolong the phar-

macological action of a drug.

Physiological variables such as gastric emptying and the degree of intestinal motility can modify the rate of absorption of a drug. Foodstuffs within the stomach may interfere with absorption by absorbing or binding a drug. The rate of gastrointestinal mucosal blood flow may possibly limit the rate of absorption in normal animals.

Sustained Action Dosage Forms

Reading papers presented at the Industrial Pharmacy Symposium on Oral Sustained Action Medication sponsored by the St. John's University College of Pharmacy, I was impressed by their quality and the straight-forward manner in which they defined the problem and described the manner in which solutions had been obtained. Even more, the papers are provocative enough to generate research ideas. One that specifically occurred to me was the possibility of using enzymes in the formulation, tablet or suspension, to provide for more effective disintegration in a chosen region of the gut. Delayed action is often accomplished by mixing the drug with a fatty material that will not be soluble in the acidic region of the stomach but will be dissolved or removed in the nearly neutral or slightly alkaline intestinal milieu. The inclusion of an esterase or lipase which is not active in an acid medium, but will quickly break down the fatty coating at higher *p*H values, could provide additional assurance of disintegration at the desired location. Even more, the enzyme plus the fatty material could be made to release the medication more rapidly than would take place in the absence of the enzyme.

From these papers also comes the thought that different derivatives of the same drug might be devised to be absorbable from different regions of the gastro-intestinal tract. This is quite apart from the derivatives now produced to hydrolyze more or less slowly and thus give prolonged action or quicker onset of activity. Since absorption seems to depend upon partition of unionized and ionized forms between lipid and aqueous phases, derivatives that are ionic at low *p*H values, such as betaines, will be absorbed in one area while succinates, ionic in alkaline media, should be absorbed elsewhere. Similar factors are probably also valid with anionic or cationic resin complexes.

Anameba

Amebiasis is estimated to occur overall in about 4 per cent of the population of the United States, but in some areas as many as 30 per cent of the inhabitants may harbor the causative ameba. This high incidence, especially in tropical and subtropical regions, underlines the potential usefulness of bacitracin against *Endameba histolytica*. Good clinical responses have been obtained with doses of 40,000 to 100,000 units of bacitracin activity daily, but costs of medication reduce the availability of the treatment. The methylene disalicylate compound of the antibiotic can be used, but effects are even more pronounced when a combination with a synthetic is used clinically. Bacitracin methylene disalicylate to provide 5,000 units of bacitracin activity is combined with 125 mg. of iodochlorhydroxyquin in each tablet of "Anameba" (Chicago Pharmacal Company); the recommended dosage, one tablet three times daily for eight days thus invloves treatment with 15,000 bacitracin units daily. Results of treatment with "Anameba" in a group of 23 carriers of *E. histolytica* were excellent, 21 being cured and remaining so on examination four months later. There was no nausea, diarrhea, or other sign of toxicity or side effects. Good results were also obtained in another study of 18 subjects.

Two Cancer Drugs

C. L. Spurt and D. M. Hayes (*South. Med. J.* 53: 1005, 1960) used uracil mustard in 18 and cyclophosphamide in 16 patients with various neoplastic diseases.

Uracil mustard seemed to be a compound with definite antitumor activity in certain neoplastic states. It showed encouraging activity against a number of lymphomas, including chronic lymphocytic leukemia, giant follicular lymphoma, reticulum cell sarcoma, Hodgkin's granuloma, and lymphosarcoma. Its activity aaginst multiple myeloma cannot be assessed now, but there seems to be some hope that uracil mustard will be helpful in this condition. There are also indications that this drug will be of use in the control of polycythemia vera and pathologic thrombocytosis is occasional patients. Uracil mustard has the same range of toxicity as other mustard compounds.

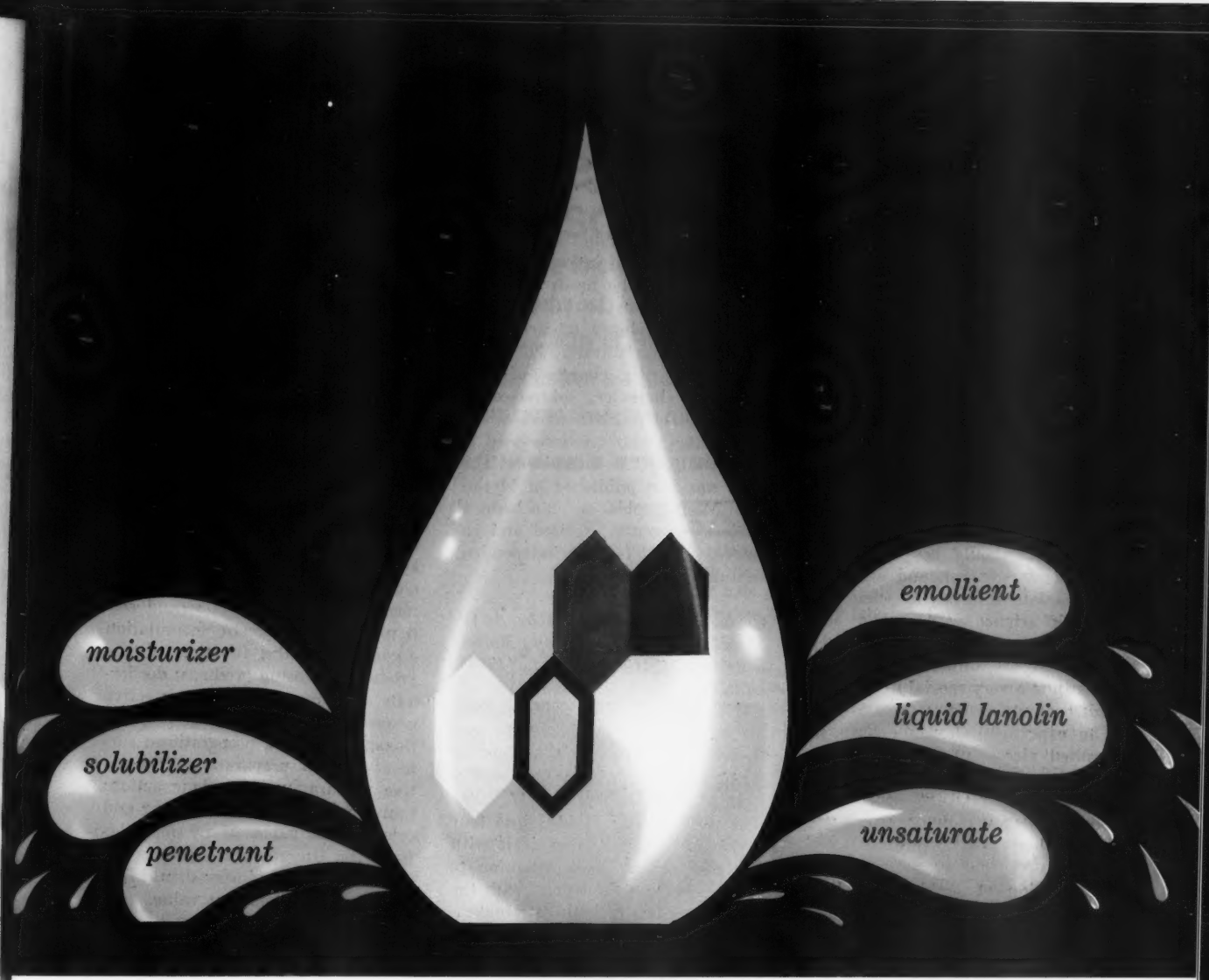
Cyclophosphamide seemed to have antitumor activity in some patients. The authors found that this drug is not strikingly effective against acute leukemia. The response of 2 solid tumors was striking enough to encourage further trial of the drug in patients with similar conditions. A less pronounced, but no less definite, response in a patient with carcinoma of the ovary was also encouraging. Although cyclophosphamide is reputed to be effective against lymphomas, no data on such patients are available at present. The toxicity of cyclophosphamide is of the same nature as that of nitrogen mustard, except that transient alopecia, heretofore an infrequent sequela of nitrogen mustard therapy, is a definite risk with cyclophosphamide.

Appetite Suppressant

Benzphetamine was superior to phenmetrazine, d-amphetamine, and placebo in an intensively analyzed, 4-way, double-blind study by A. Poindexter (*Current Ther. Res.* 2: 354, 1960) in 81 obese adults who were not put on restricted diets. There is a definite possibility that benzphetamine, given on a flexible regimen starting with 25 or 50 mg. daily, will retain its appetite-suppressant effect and will be associated with few troublesome side effects.

Weight loss, by all criteria, was superior and more persistent with benzphetamine than with the other 3 preparations.

Benzphetamine and phenmetrazine produced significantly less stimulation of the central nervous system than did d-amphetamine, and both were remarkably free of gastro-intestinal side effects. Benzphetamine was also remarkably free of dermatologic reactions. The use of benzphetamine and phenmetrazine, alone or in sequence, for as long as 22 weeks had no untoward effects on blood pressure, circulating blood picture, urinalysis results, or levels of serum glutamic oxalacetic transaminase. The incidence of side effects may be expected to be even less if benzphetamine is given in doses lower than those used in this study. Others have reported good appetite suppression with lower doses.



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Industry's Books . . .

General Endocrinology, *by C. Donnell Turner, Ph.D., Professor of biology, Duquesne University, Third Ed., Illus., 511 pp., W. B. Saunders Co., Phila., (1960), cloth,* **$9.50.**

So much new information has been acquired and concepts have changed so completely since the publication of the first edition of this work, that the author deemed it necessary to rewrite all chapters, to bring them up to date. The first edition of this book resulted from the author's strong conviction that the subject should be presented to students in general, and especially to graduate students in science, as a basic science rather than as a clinical specialty. The medical applications are important, but they constitute a very special field, which this book makes no attempt to treat. The experimental rather than the applied viewpoint has been maintained and, in the present edition, almost all clinical references have been deleted and more comparative material added.

Transactions of the Vacuum Metallurgy Conference—1959, *Edited by Rointan F. Bunshah, Associate Research Scientist, College of Engineering, New York University, New York University Press, N. Y., 212 pp., Paper binding,* **$7.50.**

This volume is the result of the third annual meeting on vacuum metallurgy held at the University Heights campus of New York University, June 1-3, 1959, under the sponsorship of the Department of Metallurgical Engineering in cooperation with the Office of Special Services to Business and Industry. This meeting was a conference at which papers on new research and advanced engineering information in vacuum metallurgy were presented.

Selective Toxicity, *by Adrien Albert, Professor of Medical Chemistry, Australian National University, 233 pp., John Wiley & Sons, Inc., New York, Second Ed. (1960), cloth,* **$5.50.**

The book begins by discussing the biochemical differences between species, which introduce the possibility of selectivity into toxicity. This is one of four introductory chapters of general interest, particularly suited to the needs of undergraduate students in biochemistry, medicine, veterinary science, pharmacy, and agriculture. These are followed by nine chapters of more advanced character, addressed to those research workers in chemistry and biology who are interested in biologically active substances. This book was first published in Methuen's Monograph's on Biochemical Subjects; but now, revised and enlarged, it appears as an independent volume.

Cosmetic Science, *Edited by A. W. Middleton, Ph.D., 327 pp., Butterworth & Co., (Canada) Ltd., (1959), cloth,* **$12.**

This is the published proceedings of the Congress organized by the Society of Cosmetic Chemists of Great Britain, held at University College, London, April 15-17, 1959. The meeting was divided into four groups. The first session dealt with analysis, paying some attention to perfumery, and the second with the quality control of both raw materials and finished products. The third session covered some of the mechanical and engineering problems connected with the manufacture of cosmetic preparations. The final session concerned the physiological aspects and the importance of cosmetics in modern civilization. This is said to be a cross-section of current international opinion, appealing to all concerned with cosmetic production and marketing.

Passport to Paradise . . . ?, *by Bernard Finch, 191 pp., illus., Philosophical Library Inc., New York (1960), cloth,* **$6.**

The purpose of this interesting book, written primarily for the general reader, is to enlighten the public about drugs, their origin, history, and uses. The story is told in a clear and lucid way. The book covers a wide range, including sexual power of drugs; drug addiction; mescalin; the Devil's Weed; alcohol; strychnine. Several chapters have been devoted to the newer drugs acting on the brain, and the relationship between them and madness has been discussed. Later chapters describe some of the more common plants used in medicine.

Kosmetologie, *by Dr. J. Stephan Jellinek, 621 pages, Dr. Alfred Huthig Verlag GMBH, Heidelberg, Germany (1959), cloth* **DM 40.**

The first section of this book, which is written in German, discusses the scientific principles underlying the manufacture and action of cosmetics, while the second section discusses the formulation and preparation of cosmetics. The general subjects first discussed are the anatomy and physiology of the skin and the hair, their external appearance, and the chemistry of keratin; surface active agents; microbiology in cosmetic; the physical form of cosmetics. The second section discusses cosmetic formulation according to the function of the product: cleansing products; deodorants and antiperspirants; protective cosmetics; skin-smoothing preparations; penetrating preparations; surface makeup preparations; decorative preparations with long action; toning preparations; perfuming and coloring cosmetics. Many formulas from the literature are given, and chemists in the industry should find the work of substantial value.

Perfumes, Cosmetics And Soaps (With Special Reference to Synthetics), *by William A. Poucher, F.P.S., F.R.P.S., Volume Three, Being a Treatise On Modern Cosmetics, Seventh Ed., Revised, D. Van Nostrand Co., Inc., Princeton, N. J., (1960), cloth,* **$8.50.**

This well-known work was first published in 1923 and is now in its seventh revised edition. The formulas and manufacturing processes have been brought up-to-date, in accordance with the advances since the Sixth Edition published in 1950. Contents include: Chapter I—Bath Preparations; II—Dental Preparations; III—Hair Preparations; IV—Hair Dyes; V—Lipsticks; VI—Manicure Preparations; VII—Rouges and Eye Cosmetics; VIII—Shaving Preparations; IX—Skin Creams and Lotions; X—Smelling Salts; XI—Sunburn Preparations; XII—Theatrical Requisites; XIII—Toilet Powders. This new edition should be of special interest to chemists engaged in this field.

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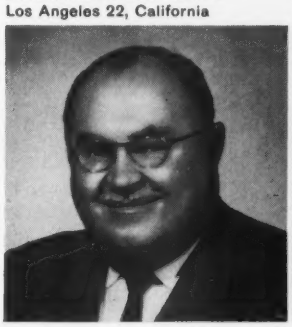

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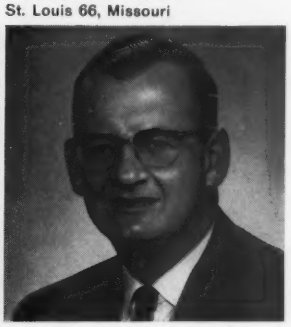

Trade Literature

Volumetric Filling Machines

Popper & Sons, Inc., 300 Park Avenue, New York City 10, have issued a catalog, #860F, which covers in 12 pages the company's line of Volumetric Filling Machines. Photographs, descriptions, and technical data are given on the entire line, with particular emphasis on table models and several new developments.

Atlas Powder

Atlas Powder Company, Wilmington, Delaware, has put out a 34-page booklet in several colors, and with photographs and drawings, which describes the company's production, its products, and research, and lists the industries that use such materials, including the cosmetic, paper and printing, pharmaceutical, plastics, and dentifrice industries.

Vitamin Preparations

Nysco Laboratories, Inc., 34-24 Vernon Blvd., Long Island City 6, New York, has issued a folder that provides a list of all its vitamin preparations (powders, capsules, and tablets), and gives for each its name, color, shape, exact content, other factors, and description.

Citrus in Medicine

Sunkist Growers, Pharmaceutical Division, 720 East Sunkist Street, Ontario, California, has introduced Citrus in Medicine with Vol 1, No. 1, to provide the pharmaceutical industry and the medical profession with information concerning the potentials of citrus and its derivatives in health and disease.

Drugstore Seminar Report

McCall's, 230 Park Avenue, New York City 17, has issued a summary of the discussion of its third drugstore seminar, this one dealing with selling cosmetics and toiletries in drugstores. The 16-page book includes photographs of the participants.

Corn in Industry

Corn Industries Research Foundation, 1001 Connecticut Avenue, N.W., Washington 6, D. C., has published Corn in Industry, a 65-page, revised and illustrated booklet describing the development of corn hybrids, the processing of corn, and its use in many products.

Dragoco Report

The most recent Dragoco Report, published in the English language in West Germany, contains the first part of an article on the chemistry of musk compounds, by Dr. Siegfried Mignat.

Merchandising Trends

Doyle Dane Bernbach, Inc., 20 West 43rd Street, New York City, has issued Planning Merchandising Strategy for 1961-1965, one in a series of merchandising reports. This describes merchandising trends now in the making which are expected to be of vital importance in the coming years. The 73-page report covers shopper rebellion against self-service, internal competition, giant retailing, leasing departments, international brands, change among mass retailers, distribution, decline in giveaway merchandising, and the waning role of the salesman.

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Skin Research

Rubefacients

Of the various rubefacients tested in 5 per cent concentration by J. B. Peterson, E. M. Farber, and G. P. Fulton (*J. Invest. Dermatol.* 35: 57, 1960), certain of the esters of nicotinic acid seem to have the strongest and most consistent activity. They seem to act on responsive skin to produce in most instances local erythema, local edema, and peripheral flare of erythema. The skin temperature elevations evoked by rubefacients seem to quantitatively parallel the extent of erythema produced. Maximal erythema usually precedes maximal temperature rise by several minutes.

Under the conditions of the foregoing study, quantitative inunction of the rubefacient ointments studied has little or no effect on the resultant cutaneous responses.

Concentration studies on chosen rubefacients indicates that rubefacient effects are not proportional to the concentration employed, at least within the range tested.

Subjects with white dermographism but without evident cutaneous disease seem not to respond with appreciable erythema to the nicotinate rubefacients. This cutaneous behavior is similar to that of patients who have atopic dermatitis and who demonstrate white dermographism as well. It is well substantiated that patients with atopic dermatitis fail to respond to tetrahydrofurfuryl ester of nicotinic acid. It seems that such subjects likewise fail to respond to other nicotinate rubefacients, namely, n-hexyl, methyl, and ethyl nicotinates.

Normal subjects show minor day-to-day variations in response to the application of nicotinate rubefacients. It is well known that one's vascular responses in terms of white or red dermographism may vary from time to time. A variation in the dermographic response has been shown to occur from day to day as the natural course of certain dermatitides evolve. Variations in response to intradermal histamine have been shown to occur from hour to hour in certain patients with atopic dermatitis as changes in their psychological orientation occur. It seems entirely feasible that minor changes in response to the nicotinate rubefacients might likewise be produced by the day-to-day physiologic variations which occur in normal subjects.

Keratolytic Acne Lotion

Acne therapy demands above all else a topical medication for the achievement of a continuous, mild, nondisfiguring, drying and peeling of the skin to remove and prevent follicular obstruction. S. Blau and N. B. Kauof (*Arch. Dermatol.* 82: 266, 1960) report experiences with a new rapid drying and keratolytic agent in the treatment of acne.

Polyoxyethylene lauryl ethers are nonionic emulsifiers. produced by the condensation of ethylene oxide with lauryl alcohol.

The specific ether used in this study is a colorless, oily liquid at 25 C that is soluble in high concentrations in distilled water and is easily dispersed in hard water.

Polyoxyethylene emulsifier alone, in concentrations up to 30 per cent, produces only a mild astringent sensation on the skin. However, with the addition of sulfur 2 per cent, zinc oxide, talc and bentonite base, a surprising synergism is noted. Marked peeling and drying takes place, which is not duplicated by any of these ingredients alone. Further preliminary clinical trials established that a concentration of polyoxyethylene lauryl ether 6 per cent and sulfur 2 per cent in a scented water washable cream base, tinted with neocalamine will produce a beneficial peeling of the acne skin in almost every case, and that the degree of peeling could be easily controlled by regulating the frequency of application of the medication. This formulation was used in the treatment of 420 patients with acne vulgaris.

Depending on the frequency of application of the medication, a satisfactory, rapid, controlled drying of the skin and hence improvement in the acne took place in almost every case.

Sixty-one patients (14 per cent) complained of discomfort due to excess drying. These effects were quickly and completely reversible.

Human Sebaceous Gland

A description of the electron microscopic appearance of the secretory and ductal parts of the human sebaceous gland is given by A. Charles (*J. Invest. Dermatol.* 35: 31, 1960).

The secretory cells are compared with a published account of corresponding cells in young mice; the composition of the secreted lipid droplets seems to be different, and they do not arise within cytoplasmic membranes. Nor is there any evidence that they arise within the mitochondria, but appear directly in the cytoplasm. The mitochondria are devoid of the opaque granules reported in the mitochondria of the mouse secretory cell.

The duct of the gland seems to be lined with a narrow band of radially-flattened cells, within which occur the compressed secretory droplets, with a little dense granular material between. It is presumed that the individuality of the droplets is maintained because of their pasty consistency. •

SPEAKING FROM THE U.S.A.

ROBERT P. T. YOUNG, B. CH. E., M.S. IN ENG., *was formerly Section Head in charge of Dentifrice Process Development, Basic Development, and Perfumes and Flavors for the Toilet Goods Division of The Procter and Gamble Company. He was with Procter and Gamble since 1941 with the exception of the six years he spent in the Navy—During World War II he was concerned with the design, manufacture, and inspection of 40 mm. ammunition; during the Korean war—propellants for rockets and missiles. A lieutenant commander, he was Head of the Test and Quality Control Division, Naval Powder Factory, Indian Head, Maryland. He received a Letter of Commendation for his contribution to the design and development of the Mark 43 solid propellant rocket grain.*

Glycerine IN DENTIFRICES

Benjamin Franklin once wrote, "Many complain of their memory, but few of their judgment." Since we can assume straight-off that readers of this article are people of good judgment, it seems quite proper to offer a memory-aid, or key-word, to use in considering the role that glycerine plays in modern dentifrice formulation. The key-word for a dentifrice formula is *BASHFUL* and all dentifrice ingredients can be classified into one of the following groups (remember the key-word):

B is for binders

A is for abrasives

S is for sudsers

H is for humectants

F is for flavors

U is for unique additives

L is for liquids

Glycerine is a humectant, and as you will see it has a rather central position in a good dentifrice formula. A humectant can affect every other ingredient, and its presence in the formula is, I believe, the principal reason the American people overwhelmingly prefer toothpaste to toothpowder. It may be of some interest in passing to note that the largest selling dentifrice in America (1959 figures) has the highest glycerine content.

Binders

B is for binders and binders stabilize the paste. All binders provide highly viscous aqueous systems, and the best are quite thixotropic or gelatinous in nature. The purpose of these stabilizers is to prevent the separation or stratification of the various ingredients used, and when one considers the diversity of these ingredients—from heavy, solid, inorganic abrasives to light liquid, organic essential oils—one realizes the magnitude of the binder's task.

One of the earliest binders used was glycerite of starch. This was followed by various natural gums: karaya, gum arabic, or gum tragacanth. Today, the principal attention by dentifrice formulators is directed toward seaweed derivatives (Irish Moss) and toward the synthetic celluloses. (1) In addition to these organic binders, bentonite, a native, colloidal, hydrated aluminum silicate, and Veegum, a complex colloidal magnesium aluminum silicate, have been recommended for use. (2)

Almost every edible thickening agent can be considered to be a potential dentifrice binder. A simple screening test to determine the potential usefulness of a material as a dentifrice binder is to make a 1% solution of it in a 50:50 glycerine-water solution. If the binder is incompatible in this system (and many natural materials such as locust bean, guar gum, etc. are), it is not likely to be a very satisfactory dentifrice ingredient.

Gershon et al. (2) mention that one of the best ways to make a toothpaste is to disperse the binder first in the humectant and then add this slurry to the aqueous phase. In this type of processing an essentially anhydrous system is needed for best dispersion, and glycerine is ideal.

In choosing a binder, particular attention must be paid to its interaction with all other ingredients. Since most abrasives contain trace quantities of cations (calcium or magnesium ions), these can interact at available sites on the binder molecule and cause firming or lumping on long-term storage. Some binders, particularly Irish Moss extractives, act synergistically with the sudsers to produce a more stable foam on brushing. It is necessary to balance the binder with the humectant to arrive at the ideal viscosity, and also to produce a glossy, short-textured product. Finally, the binder must be completely bland in flavor and odor, and it must be compatible with the unique additives used in the formula.

Abrasives

The purpose of dentifrice abrasives is to remove the stains which form on teeth. Ideally, these materials should accomplish this without damaging the soft part of the tooth structure (dentin) which is often exposed near the gum line.

The literature covering dentifrice abrasives is most fascinating. Historically, such exotic materials as pulverized eggshells, rouge, charcoal, wood sawdust, silicon carbide, and powdered cuttlebone have been mentioned. (3) The materials recommended for use today are much more commonplace consisting of :

Dicalcium phosphate	Magnesium hydroxide
Tricalcium phosphate	Diammonium phosphate
Calcium carbonate	and similar materials

Kuever (4) patented the use of insoluble sodium metaphosphate. Phillips and Van Huysen (5) reported that when this material was mixed with calcium phosphate some polishing action occurred. Special abrasives have also been designed for special purposes.

The interaction of humectants with abrasives is quite important to the "mouth-feel" of the dentifrice. Great care must be exercised to secure the proper balance between "chalkiness" on one end of the scale and "sliminess" on the other. Interestingly enough, there is a profound difference between humectants in this respect and glycerine seems to offer more flexibility in formulation than the others.

It is known that glycerine reduces the abrasiveness of the abrasives used without substantially affecting their cleaning power.

Sudsers

Longfellow (7) reports that soap has been replaced by synthetic anionic surface active agents in all the major brands of dentifrice. The principal sudsers in use today are:

Sodium lauryl sulfate
Sodium N-lauroyl sarcosinate
Sodium lauryl sulfoacetate
Dioctyl sodium sulfosuccinate
Sodium salt of sulfonated coconut monoglyceride

All of these materials must be highly purified to prevent imparting undesirable (mostly bitter) flavor notes to the dentifrice.

Citrus fruit and other acid foods tend to have a bitter taste if eaten soon after the teeth are brushed with a dentifrice containing a synthetic surfactant. (8) Sanders (9) has obtained a patent on blends of sodium lauryl sulfate (1 part) with monoglyceride sulfonate (2 to 5 parts) which are quick sudsing and have no more effect on the taste of orange juice than the pure monoglyceride sulfonate.

One of the differences between soap and synthetic surfactant is the feel or "slip" of the foam produced. Over the years people have become accustomed to the soft, slippery feel of soap, and the synthetics seem harsh or "squeaky-clean." Glycerine does much to overcome this objection—foams of systems containing synthetic surfactants are markedly smoother and more stable if glycerine is added.

Humectants

The principal purpose of using humectants in a dentifrice is to prevent the paste from drying out. The most serious type of dry-out occurs at the tube nozzle particularly when the cap has been removed and lost. Most pressure-packed formulae are particularly high in humectant level since normally no cap is used and because the polyethylene nozzle is rather readily permeated by air and water vapor.

When considering humectants for dentifrice only three materials are usually mentioned:

Glycerine **Propylene glycol**
Sorbitol

Propylene glycol is reported to have a slightly acrid taste. (10) It has not been widely used.

In considering the relative merits of glycerine or sorbitol as humectants for toothpaste, it is fair to state that glycerine offers all the advantages of a near anhydrous liquid. Sorbitol, which is a solid when anhydrous, tends to produce firmer pastes. Glycerine also has the tremendous advantage of being the traditional humectant used, and its interaction with all of the other ingredients in a dentifrice is established and well-known.

Flavor

One of the most important consumer properties of a dentifrice is its flavor. The flavors of the leading dentifrices in the American market are fundamentally mint, wintergreen, or root beer in type. A dentifrice flavor consists of volatile essential oils (peppermint oil, spearmint oil, methyl salicylate, menthol, anethole, etc.) and crystalline components—saccharin, cyclamate, salt, etc. The base stock also contributes flavor, and the most advantageous of the ingredients in the base stock, from a flavor point of view, is the glycerine. Carr, Beck, and Krantz (11) have furnished the following table:

Relative Sweetness of the Sugar Alcohols
(Sucrose Taken as 100)

Glycerol	108
i-Erythritol	238
Pentaerythritol	110
d-Mannitol	57
d,-l-Sorbitol	54
i-Dulcitol	74
Inositol	50

From the above, it appears that glycerine is twice as sweet as sorbitol. Mannheim (12) reports that a very popular dentifrice used in Europe during the '30s contained 38 per cent glycerine and required no, or very little, saccharin for sweetness.

Unique Additives

Therapeutic dentifrices have received increasing attention during the past ten years. They owe their performance to ingredients we have termed "unique additives."

The list of unique additives is a long one. Those intended to reduce caries have included:

Ammonia salts and urea compounds
to neutralize mouth acids.

Sodium N-lauryl sarcosinate
to act as an anti-enzyme.

Sodium oxalate
to build an insoluble film on teeth.

Hexachlorophene
to destroy mouth bacteria.

Stannous fluoride
to reduce the solubility of tooth enamel in acid. (13)

Tyrothricin
to act as a general antibiotic.

The search for unique additives has even gone as far as Ora S. Flower's (14) idea of adding living organisms, *Bacillus alcaligenes*, to the paste and thus inoculate the mouth with alkaline-producing bacteria.

New Zealand has the highest incidence of dental caries in the world and Drs. Irwin and Leaver (15) have clinically tested tetradecylamine acetate there.

Unique additives have been recommended for purposes other than reducing tooth decay. Mouth odor is a particularly important problem, and toothpastes green with chlorophyll were once in vogue. It is sometimes necessary to add a preservative to protect the paste itself from microbial attack and ethyl p-hydrozybenzoate at 0.1 per cent of formula has been recommended. (16) The removing of stain from the teeth by the addition of dextran to the formula was recommended by Russell and Nelson. (17)

Glycerine is a particularly valuable ingredient in a dentifrice when its interplay with the unique additives is considered. Many of these materials are reactive chemicals and more or less soluble in water. Instability of these actives through chemical reactivity of one type or another becomes a serious problem as the pastes age. One of the best ways to reduce this reactivity is to replace as much of the water as possible with glycerine.

Liquids

The common liquid in all dentifrices is water. Deionized or distilled water is recommended to minimize the possibility of color or flavor changes.

Small amounts of mineral oil have sometimes been used, principally to make it easy to extrude the paste from the tube. It is quite obvious that mineral oil puts a tremendous load on the sudsers.

Humectants and water make up the large bulk of the liquid phase of the dentifrice. The relative amounts used have a marked effect on the physical as well as the brushing properties of the paste. A good place to start in designing a new formula is 50:50 glycerine-water.

SUMMARY Using the key-word, BASHFUL, the formulation of a dentifrice has been discussed. It has been shown that glycerine interacts with each of the other ingredients, and that it is indeed an important and beneficial component of a fine dentifrice.

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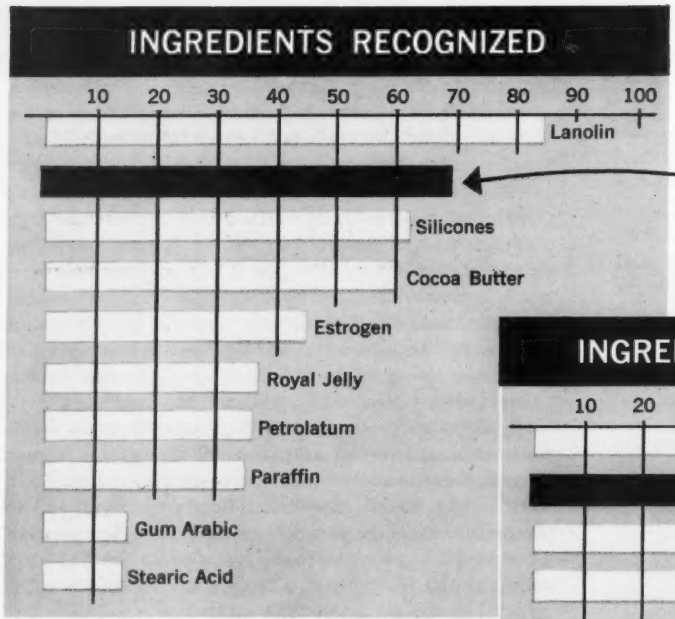

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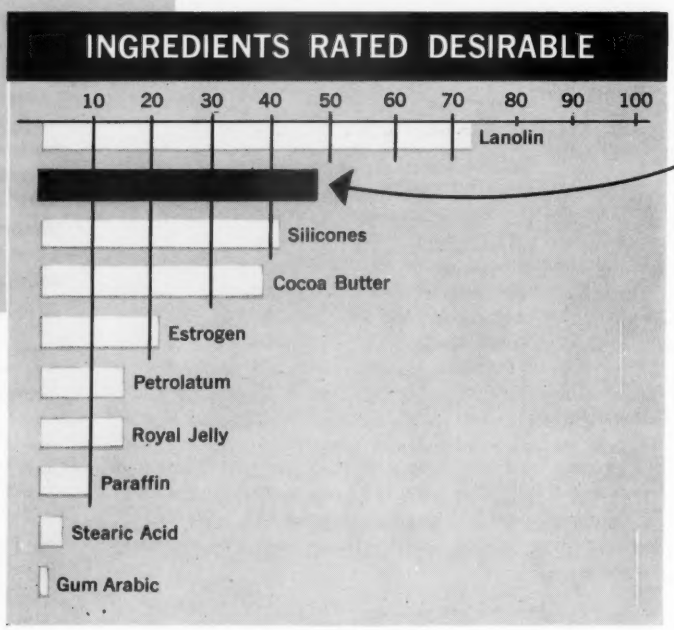

Consumer panel votes YES! for Glycerine

Here again is evidence that "Contains Glycerine" is a phrase that promotes sales on any label. A panel of women having broad geographic and economic distribution recently placed glycerine second only to lanolin as an ingredient they recognized and rated desirable in toilet goods.

The soothing softness produced by Glycerine and Rose Water, Glycerine Soap and other long familiar products has registered with millions of American women. In addition, glycerine offers an unmatched combination of desirable propertes . . . controls body and consistency, lubricates, prevents settling, resists hardening and prolongs product life.

Glycerine deserves a feature spot on your label just as your product deserves glycerine. We'd be glad to supply technical information. Address your request to the Glycerine Producers' Association, 295 Madison Avenue, New York 17.

SOOTHING WORDS

that give sales a lift

COMING EVENTS . . . . .

OCTOBER

14-20 **National Wholesale Druggists' Assn.**, annual convention, Americana, Bal Harbour, Fla.

16-19 **Pharmaceutical Manufacturers Assn.**, Financial Section, Boca Raton Hotel, Boca Raton, Fla. (Dr. Karl Bambach, P.M.A., 1411 K Street, Washington 5, D. C.)

16-19 **Pharmaceutical Manufacturers Assn.**, Public Relations Section, The Greenbrier, White Sulphur Springs, West Virginia (Dr. Karl Bambach—see above.)

17-19 **American Oil Chemists' Society**, fall meeting, Hotel New Yorker, N. Y. C.

17-20 **American Dental Assn.**, annual meeting, Sports Arena and Statler-Hilton Hotel, Los Angeles, Calif. (A.D.A., 222 E. Euperior St., Chicago 11, Ill.)

19 **American Society of Perfumers**, open meeting, Advertising Club, N. Y. C. (Dorothy A. Douglass, A.S.P., 630 Fifth Avenue, N. Y. C. 20)

19-21 **Parenteral Drug Assn.**, annual convention, Statler Hilton Hotel, N. Y. C. (P.D.A., 1420 Snyder Avenue, Philadelphia 45, Penna.)

19-29 **International Plastics Exhibition, "macroPlastic,"** Exhibition Halls, Utrecht, The Netherlands.

23-27 **National Assn. of Retail Druggists**, annual convention, Municipal Auditorium, Denver, Colo. (Jack E. Simmons, N.A.R.D., 306 Kittredge Bldg., Denver, Colo.)

25 **Assn. of Consulting Chemists & Chemical Engineers**, annual meeting and dinner, Hotel Shelburne, N. Y. C.

25-26 **Pharmaceutical Manufacturers Assn.**, Pharmaceutical Contact Section, Washington Hotel, Washington, D. C. (Dr. Karl Bambach—see above.)

26-27 **Pharmaceutical Manufacturers Assn.**, Production and Engineering Section, Seaview Country Club, Absecon, N. J. (Dr. Karl Bambach—see above.)

26-28 **Annual Symposium on Antibiotics**, sponsored by *Antibiotics and Chemotherapy, and Antibiotic Medicine*, Mayflower Hotel, Washington, D. C.

31 **Packaging Institute, Inc.**, annual national packaging forum (through November 2) Statler Hilton Hotel, N. Y. C. (Chas. A. Feld, P.I., 342 Madison Ave., N. Y. C. 17)

31 **American Management Assn.**, course in packaging (through November 4), Hotel Astor, N. Y. C. (A.M.A., 1515 Broadway, N. Y. C. 36)

NOVEMBER

2 **Society of Cosmetic Chemists**, New York Chapter, monthly meeting, Hotel New Yorker, N. Y. C. (Dr. Saul Bell, S.C.C., 2 East 63rd St., N. Y. C. 21)

3 **Pharmaceutical Advertising Club**, luncheon meeting, Hotel Roosevelt, N. Y. C. (D. Lindsay, P.A.C., Suite 608, 489 Fifth Ave., N. Y. C.)

8 **Society of Cosmetic Chemists**, Chicago Chapter, Chicago, Ill.

12-19 **Pan-American Congress of Pharmacy and Biochemistry**, Santiago, Chile

14 **Salesmen's Assn. of the American Chemical Industry**, annual sales clinic, Hotel Roosevelt, N. Y. C. (S.A.A.C., 60 East 42nd. St., N. Y. C. 17)

14-16 **Pharmaceutical Manufacturers Assn.**, Research and Development Section, The Cloister, Sea Island, Ga. (Dr. Karl Bambach, P.M.A., 1411 K Street, Washington 5, D. C.)

16 **American Society of Perfumers**, open meeting, Advertising Club, N. Y. C. (Dorothy A. Douglass, 630 Fifth Ave., N. Y. C. 20)

28 **Glass Container Manufacturers Institute**, semi-annual membership meeting (through December 1), Boca Raton Hotel, Boca Raton, Fla. (G.C.M.I., 99 Park Ave., N. Y. C. 16)

29 **Society of Cosmetic Chemists**, annual meeting, Hotel Biltmore, N. Y. C. (S.C.C., 2 East 63rd St., N. Y. C. 21)

30 **Toilet Goods Assn.**, Scientific Section, Waldorf-Astoria Hotel (Kathryn Fitzpatrick, 1270 Avenue of the Americas, N. Y. C. 20)

DECEMBER

1-2 **American Medical Assn.**, clinical meeting, Washington, D. C.

5-7 **Pharmaceutical Manufacturers Assn.**, eastern regional meeting, Waldorf-Astoria Hotel, N. Y. C. (Dr. J. O'Neill Closs, 1411 K Street, N.W., Washington 5, D. C.

5-8 **Chemical Specialties Manufacturers Assn.**, annual meeting, Hollywood Beach Hotel, Hollywood, Fla. (C.S.M.A., 50 East 41st St., N. Y. C. 17)

8 **Pharmaceutical Advertising Club**, luncheon meeting, Hotel Roosevelt, N. Y. C. (D. Lindsay, P.A.C., Suite 608, 489 Fifth Ave., N. Y. C.)

12-14 **Pharmaceutical Manufacturers Assn.**, mid-year meeting, Waldorf-Astoria Hotel, N. Y. C. (Dr. J. O'Neill Closs—see above.)

12-16 **Industrial Building Exposition and Congress**, Coliseum, N. Y. C. (Clapp & Poliak, Inc., 341 Madison Ave., N. Y. C.)

27-30 **American Assn. for the Advancement of Science**, Pharmacy Section Meeting, Hotel Roosevelt, N. Y. C. (John E. Christian, Secretary, Pharmacy Section, School of Pharmacy, Purdue University, Lafayette, Ind.)

FEBRUARY 1961

8-10 **Pharmaceutical Manufacturers Assn.**, Law Section, Boca Raton Club, Boca Raton, Fla. (Dr. Karl Bambach—see above.)

13-15 **Pharmaceutical Manufacturers Assn.**, central regional meeting, Edgewater Beach Hotel, Chicago, Ill. (Dr. J. O'Neill Closs, P.M.A., 1411 K Street, Washington 5, D. C.)

20-21 **Pharmaceutical Manufacturers Assn.**, western regional meeting, Ambassador Hotel, Los Angeles, Calif. (Dr. J. O'Neill Closs—see above.)

MARCH 1961

1-3 **Pharmaceutical Manufacturers Assn.**, Medical Section, Ponte Verdra Club, Ponte Verdra, Fla. (Dr. Karl Bambach—see above.)

8-10 **Pharmaceutical Manufacturers Assn.**, Medical Section, Ponte Vedra Club, Ponte Vedra Beach, Fla. (Dr. Karl Bambach—see above.)

21-30 **American Chemical Society**, spring meeting, St. Louis, Mo. (A. T. Winstead, A.C.S., 1155 Sixteenth St., N.W., Washington 6, D. C.)

20-31 **Purdue Univ. Industrial Packaging Institute**, industrial packaging short course, Purdue Univ., Lafayette, Ind. (Mark E. Ocker, Memorial Center, P.U., Lafayette, Ind.)

MAY 1961

2-9 **International Packaging Exhibition**, Amsterdam, Holland (Verpakkingsbeurn, Tesselschadestraat 5, Amsterdam, Holland) ●

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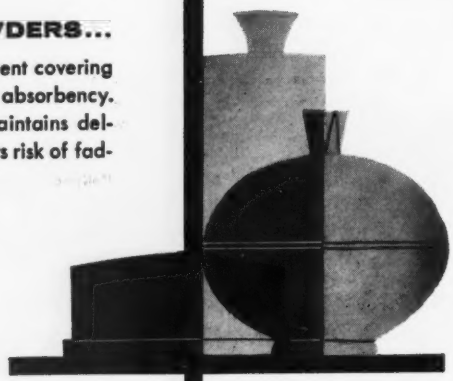

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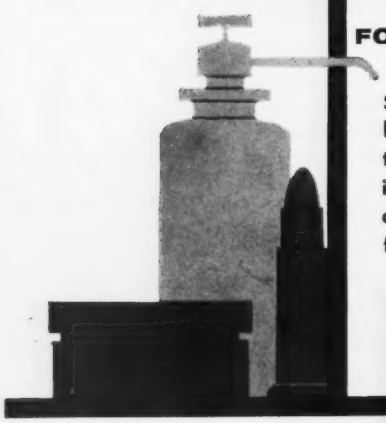

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(*Continued from page 530*)

notice that, in most cases, even twice the amount used for the refined lanolin solutions is insufficient to mask the odor of U.S.P. lanolin. On the other hand, if you use for the solutions of refined lanolin the amount necessary to cover the odor of U.S.P. lanolin, the odor of the refined lanolin is clean and far superior to the other.

From this simple experiment several conclusions may be drawn.

1. If you are price-conscious and if you use a perfume costing about $10.00 per pound, which is a low average for this kind of perfume, you can easily calculate that the difference in price of the lanolin is compensated for by the economy of using less perfume.

2. If you are quality-conscious, the odor strength of your preparation will show better for a longer period of time, as proven by shelf tests, accelerated or otherwise.

3. In all cases, there will be an improvement in odor and in color, which carries through in solutions and in emulsions. The ultimate quality will be greatly improved throughout. At what cost? In the first case, nothing. In the second case, at a concentration of 10 per cent lanolin in the finished formula, four-tenths of a cent per pound, or five cents per two-ounce jar.

All raw materials that could give trouble by discoloration or odor development from aging should be selected by competitive testing. You will find that the possible increase in cost of the finished preparation will be minimal. There are greater fluctuations in the costs of containers, wrappings, and labels, all of which are taken as a matter of course by purchasing departments.

The worries of the cosmetic chemist are numerous. Why not eliminate at least some by using the best available materials?

DIHYDROXYACETONE

(*Continued from page 463*)

known to condense and polymerize to yield dark-colored melanoidins.

Melanoidins are exceedingly complex in composition and their structures to date have defied elucidation. It is quite probable that none is a single compound.

It must be recognized that the brown coloration produced by dihydroxyacetone with the skin is a melanoidin reaction and that this is not the same compound(s) or process as the natural occurring melanins occurring after exposure to ultra-violet light.

The stain produced on the skin by dihydroxyacetone does not appear until three to six hours after application, and herein lies one of the difficulties of its

(*Continued on page 544*)

Readers' Questions . . .

Preserving Cosmetics: *Occasional jars of cream or bottles of lotions that we produce show signs of deterioration—discoloration, emulsion breakdown, odor changes—which seem to be due to ineffective preservation; can you assist us with some advice as to how we may overcome these difficulties?* BROOKLYN.

Apart from internal incompatibility situations, which should be readily avoided by care in developing a formulation, major causes of trouble with cosmetics and toilet preparations are attack by micro-organisms and attack by air. A cosmetic emulsion, liquid or cream, involves the breakdown of an oil into very small droplets, with enormously increased surface. Some of these oils are sensitive to air in their original state and thus become even more liable to destructive oxidation after emulsification. The number of antioxidants available for use is limited, but a choice can be made from butylated hydroxyanisole and toluene, gallic acid esters, sorbic acid, and probably a number of proprietary products that are effective and acceptable for use in cosmetics. Some of these compounds may cause discoloration if improperly used, others may be ineffective at too high or too low a *p*H, so that choice must be made for each individual preparation, and then tests conducted.

A similar situation holds for preservatives, which must also be selected in relation to the specific formulation. The overwhelming choice seems to be one or a combination of esters of p-hydroxybenzoic acid. These esters are very useful preservatives, but may on occasion form inert complexes with other cosmetic ingredients and have no effect in retarding the growth of bacteria. Every cosmetic preparation should contain a preservative and usually an antioxidant, chosen from those known to be harmless to the skin. These ingredients, especially because of the small concentration used, must not react with other components in the formula, and finally, they should be tested to determine that they are effective.

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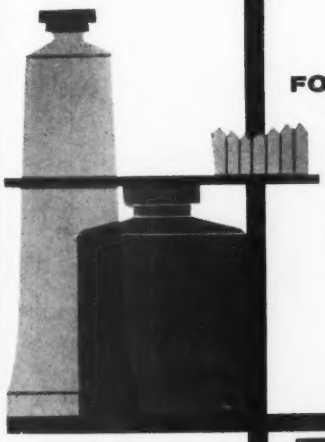

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(Continued from page 542)

use, namely, it is not known what has been accomplished until after a number of hours after it is done. At this point it is too late to undo it. The color reaction of dihydroxyacetone with the skin is apparently a nonspecific protein reaction of dihydroxyacetone and keratin.

Since we are dealing with the integument of the body in this reaction, it is necessary to consider its composition and structure.

The epidermis, which is specifically involved, may be considered to be composed of four layers. These layers are (1) the horny layer or the stratum corneum, which consists of dead scales of keratinized material; (2) the stratum lucidum, whose cells contain eleidin, which is formed during the process of keratinization; (3) the stratum granulosum, in which layer the epithelial cells die and keratohyalin appears; and (4) the stratum germinativum, which is adjacent to the derma or corium. The cells of the outer or first layer are constantly being shed (desquamated) and are replaced constantly by cells from the deeper layers of the epidermia.

Since the epidermis varies in thickness over various parts of the body and layers of epidermis containing keratin are thicker in calloused areas and certain wearing surfaces of the body, these react to a greater extent to give more intense color than surfaces where the skin is thinner, that is, the planer surface of the forearm. It has been noted also that other proliferations of the epidermis such as warts show a marked reaction with intense dark color which causes them to be conspicuous when treated with dihydroxyacetone.[19] Scar tissue, on the other hand, does not react to the extent that normal skin does and, as a result, scars show up as light-colored or white areas against the dark background of dihydroxyacetone-stained skin. Certain scaling skin diseases also reveal much lighter areas, delineating the affected parts. Different individuals react with varying degrees to dihydroxyacetone, giving a great range of tan coloration as a result of application. Generally, blondes with thin skin and less keratin and melanin give less tanning than thicker-skinned brunettes.

Although hair, nails, and skin are all made up of albuminoid protein loosely termed keratins, nails and hair do not react as readily as skin, which is a soft protein and more porous. While concentrations of dihydroxyacetone of 5 to 10 per cent do not react readily with nails, strong solutions (70 to 90 per cent) usually produce some yellow to tan color with a single application. Blonde hair is noticeably affected by several applications of a 5 per cent solution and turns a reddish brown. Brunette hair is affected but the change is less easily discernible because of the dark color. Upon several applications, under close observation, a yellowish cast will be seen.

Although there are individual differences in the depth of color produced in various persons, it is not

possible, even with repeated, numerous applications, to achieve a reddish-brown coloration deeper than the usual sun tan. It is questionable if darkening to the extent produced in dark-skinned people can be produced by dihydroxyacetone. Certain individuals resist tanning by dihydroxyacetone to the extent that they are virtually unaffected.

Increasing concentration gives more intense coloration per application.

Since the skin is usually difficult to wet because of natural oils secreted by the sebaceous glands, spotting or blotching because of uneven wetting may occur, unless the skin is thoroughly cleansed. The use of ethyl or isopropyl alcohol or acetone incorporated in the aqueous solutions of dihydroxyacetone aids in cutting these skin oils and affording better contact of the dihydroxyacetone solution and the skin. This produces a more uniform effect. It has also been demonstrated[19] that the tanning reaction is a function of *p*H. Acid solutions produce a more rapid and darker reaction than neutral solutions. The coloration decreases with decreasing acidity. At a *p*H of 8.0 and over, no reaction is obtained.

Emulsified bases having an acid reaction give good results. These have the ability to provide good skin contact, since they emulsify skin oils and make for uniform contact and an even reaction.

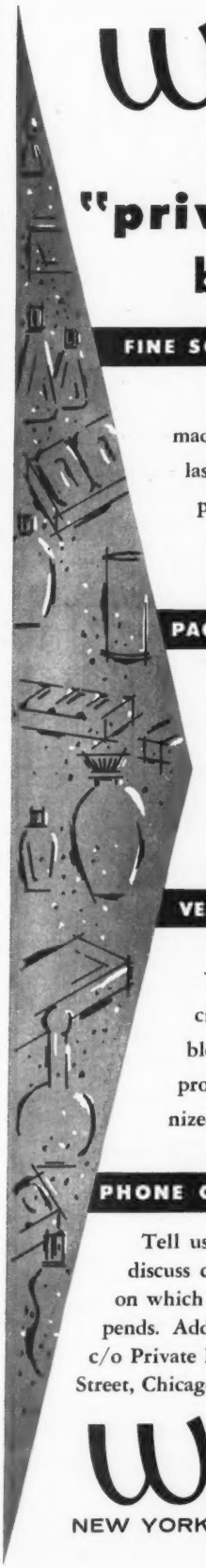
Glycerin and glycols inhibit the reaction of dihydroxyacetone with the skin. This may be due to competitive affinity of the polyhydroxy compounds and the dihydroxyacetone for the keratinous tissue.

Emulsified bases as vehicles for dihydroxyacetone give better results than hydroalcoholic or aqueous solutions in providing more rapid and more uniform coloration. They have the further advantage of being nondrying to the skin. Their emollient action and unctuous nature impart a softer appearance to the tanned skin and their greater viscosity provides more dihydroxyacetone per application than alcoholic solutions. Another disadvantage of alcoholic or aqueous solutions is that, because of their low viscosity, they have a tendency to run. This produces streaks in the tan after color develops and these are difficult to eliminate even with repeated additional applications. This is not encountered with emulsified bases properly formulated.

The addition of surfactants facilitates the reaction, probably by wetting the skin more completely and overcoming the lyophobic effect of the sebaceous secretions. Anionic and cationic surfactants are more efficient for this purpose than nonionic compounds.

The addition of so-called skin penetrating agents such as isopropyl myristate and squalene had no effect on the rate or quality of tanning.

When application of dihydroxyacetone is discontinued, the synthetic tan produced fades and disappears with desquamation of the epidermis. The affected keratin sloughs off and the natural skin color returns with the appearance of new, unaltered epidermis. The time required after the final applica-



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tion for complete loss of synthetic tan varies from eight to 14 days, depending on the site and the individual. Surfaces which are frequently washed, such as the hands, arms, and face, lose their color more rapidly than the back, chest, and legs.

In order to understand the basic differences between chemical tanning of the skin by dihydroxyacetone and the natural tanning resulting from exposure to ultraviolet rays of sunlight, the latter process should be considered.

The tanning or darkening of the skin following exposure to sunlight is due to the accelerated formation of cutaneous melanin pigmentation.[20] Brown melanin pigment is formed in specialized dendritic cells known as melanocytes. These are found dispersed in the basal layer of the epidermis. Cytoplasmic granules in these cells produce a copper-containing enzyme, tyrosinase, which causes oxidation of the amino acid tyrosine to melanin pigment, through a sequence of reactions described by Raper et al.[21] The melanin pigment is a polymer united with the proteins of the melanin granules. Normally, the enzyme tyrosinase is believed to be kept in a state of partial inhibition and can be released or activated by a number of pigmentogenic factors, including ultraviolet irradiation. Melanin can protect against ultraviolet effects, not only by its ultraviolet screening action, but also chemically in acting as a reservoir or trap for photoactively produced electrons or reactive radicles,[22] since melanin itself has stable free radicle properties.[23] Melanin pigment is gradually swept up from the epidermis to the surface of the skin and is shed from it in a more or less continuous physiological current of epidermal regenerative proliferation, keratinization, and desquamation.

In true sun tanning, three phases characterize the process:

(1) An immediate tanning effect in which darkening of the skin appears in a few minutes after exposure and reaches a maximum in less than an hour. This immediate tanning is brought about by the long wave lengths of the ultraviolet spectrum at about 3400A.[24] This reaction is thought to result from direct photo-oxidation of preformed, reduced melanin to darker oxidized melanin.

(2) Delayed tanning effect: This occurs several days after exposure to the sun and depends on the upward migration of melanin granules in the epidermis.[25]

(3) True tanning effect. The final and most important factor in the sun tanning process is the stimulation of formation of melanin in the skin. This is true tanning and is brought about by the same ultraviolet spectrum that produces sunburn. It begin about two days after exposure.[26] It reaches a maximum in two or three weeks after exposure, and begins to fade in about one month.

In summary, it may be said that the synthetic tan produced by dihydroxyacetone may be acquired more quickly than a normal sun tan and that it is

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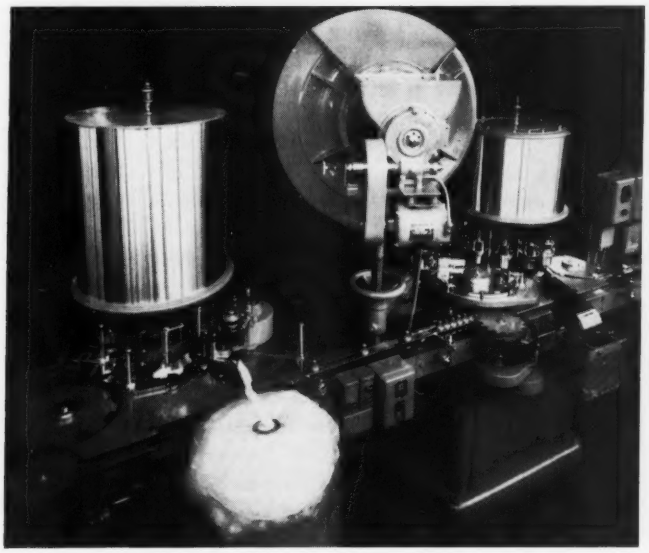

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also lost more rapidly. It is, of course, produced by an entirely different mechanism than normal sun tan and does not always simulate the natural tan. In some individuals, dihydroxyacetone produces a yellow or jaundiced coloration.

While there seems to be no danger associated with it, it does not give the feeling of increased health, physical fitness, and well-being which people experience after moderate exposure to sunlight.

REFERENCES

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DESIGN OF SUSTAINED-ACTION FORMS

(Continued from page 465)

the rate at which it is absorbed.

Biologic half-life (absorbtion-distribution-excretion kinetics). For rapidly absorbed drugs, one of the most important factors requiring consideration is the biologic half-life ($t_{1/2}$) of the plain drug.[5] Biologic half-life may be defined as the time required for the body to dissipate one-half the drug activity after the drug has been absorbed and has attained "diffusion equilibrium." A drug's biologic half-life depends somewhat on the biochemical make-up of an individual and may vary slightly between different people, or for the same person at different times. The half-lives of some drugs appear to vary with the dose or with the test used for determining it, and may be inconstant over wide tissue concentrations of drug. Thus, when one uses the term, the conditions under which its numerical value was determined must be described. Also, for the highest pharmaceutical relevance, the test used to determine biologic half-life should be pertinent to the therapeutic activity for which the drug is to be used. It appears that a biologic half-life determined from blood or urine studies sometimes may have a different value than one determined from pharmacokinetic studies. Also, a drug's half-life may vary markedly from one animal species to another.

The problems of determining tissue-drug concen-

trations, different intensities of pharmacologic activities, and biologic half-lives and their related objective performance indexes is further complicated by the need for more sensitive analytical methods to measure tissue or body fluid content of drugs, by the fact that some active drugs are metabolized to active substances in the body, and by the need for better graded pharmacologic response tests. Drugs, when administered in therapeutic doses, may often yield very low blood and other tissue concentrations. Microanalytical techniques that are specific and precise are required for a quantitative determination, to obtain an accurate understanding of their absorption, distribution, and excretion. Analytical techniques, such as vapor-phase chromatography, liquid-liquid counter current extraction, radio-chemical and other relatively new methods, offer much promise for a better understanding in this field. They may provide a better approach to the pharmaceutical design and evaluation of drug products; however, the multitude of drugs on which studies could be done, the complexities of such studies with human subjects, and the appreciable time and cost involved have made progress slow in the application of these methods to pharmaceutical problems.

We were fortunate in 1954 to have started work in the Smith Kline and French Laboratories on the development of a sustained-release form of sulfaethidole (sulfaethylthiadiazole or SETD), a compound with good analytical procedures available for its measurement in body fluids. We made our first intensive studies of biologic half-life with the "sulfa" drugs, and were able to demonstrate the value of absorption-distribution-excretion data and the biologic half-life concept to calculation of sustained-release dosage form design, and to *in vivo* evaluation of a drug's performance characteristics in various types of products. In 1956, when a sustained-release form of SETD, was marketed, we began the preparation of a series of articles[1, 5, 7-11] describing the biologic half-life concept as it applies to pharmaceutical problems, and illustrating measurements made in human subjects. The articles describe the kinetics of absorption and excretion of SETD and show how these data were applied to the problems of this product development study.

The theoretical implications of absorption-excretion kinetics to the design of sustained-release dosage forms and regimens is understood rather well; however, the experimental implementation of theory has been difficult. Therefore, practical published information in this field is still quite meager, especially in the area of pharmacokinetics,[6] where the performance indexes of pharmacodynamic drugs are usually determined by pharmacologic graded response tests. The future looks exciting for the research workers who are investigating this field. It promises a better understanding of drug absorption, excretion, and distribution, and points the way to a better practice of pharmacy, especially as it applies to the develop-

ment and evaluation of sustained-action dosage forms. As our knowledge in this field grows, we may be forced to modify some of our present views on the biologic half-life concept, but I am convinced that our line of study will make us better able to cope with problems of sustained-release product design and evaluation. This concept needs to be, and no doubt will be, considered further in future work on the selection of doses and regimens of all dosage forms.

At this juncture I would like to present some illustrative experimental data that indicate ways in which information on biologic half-life may be obtained, interpreted, and applied.

Figure 2 is a plot of blood concentrations observed in a human subject who received oral and intravenous doses of sulfaethidole (SETD). Several relationships may be noted.

1. After allowing about one hour for distribution equilibrium of drug into the tissues following an intravenous dose, a straight-line fall-off of blood concentrations is depicted. Half-life is about eight hours.

2. The fall-off curve is approximately exponential in the two- to ten-hour time interval. This is a characteristic disappearance pattern exhibited by numerous drugs in a therapeutic blood concentration range. Over broader time intervals such plots often show departure from linearity.

3. After the oral dose, blood concentrations rise rapidly. Ultimately a peak concentration is achieved, after which the fall-off curve has about the same slope as that observed with the intravenous dose. The time that the oral dose curve first parallels the intravenous dose gives a good indication of the time required for absorption of the oral dose.

Exponential excretion is describable by the equation[5]

$$\log C = \frac{-kt}{2.303} + \log C_o \qquad (1)$$

where C = blood concentration at any time
k = specific velocity constant for drug elimination
t = time
C_o = apparent zero time blood concentration (fictive concentration) which fits the straight line semi-log plot of the blood concentration data.

The drug performance indices, k and $t_{1/2}$, bear a reciprocal interrelationship expressed by

$$k = \frac{0.693}{t_{1/2}} \qquad (2)$$

In practical studies, $t_{1/2}$ is readily determined

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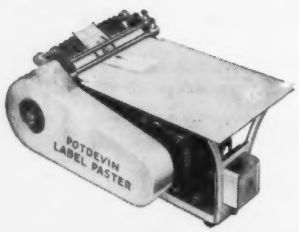

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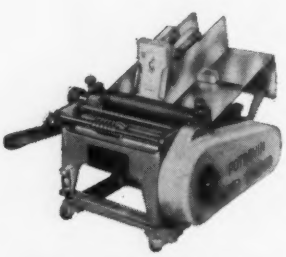

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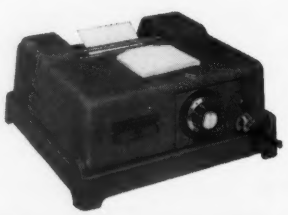

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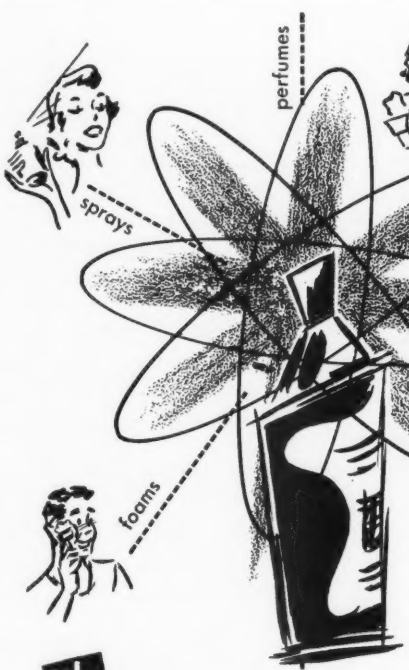

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graphically from a plot of C versus t, and, in turn, k can be determined from Equation 2.

If a drug has a $t_{1/2}$ of, for example, 4.6 hours, it will have a k of $0.15^{-hr.}$ (that is, 0.15 reciprocal hours). More literally, the value of k indicates that at any instant the rate of disappearance of the drug in the body at that time is 15 per cent per hour. In terms of the biologic half-life, this means that a unit quantity of drug in the body will have decreased to ½ unit in 4.6 hours, to ¼ unit in 9.2 hours, to ⅛ unit in 13.8 hours, etc., as long as the exponential disappearance rate is maintained.

Release requirements of dosage form. Usually the objective in making a sustained-action dosage form is to provide an initial amount of readily available drug so that it becomes effective rapidly, and a maintenance portion which upon continuous release is absorbed in the tract at a rate that compensates for the loss of drug activity through excretion and metabolism. The rate at which the maintenance portion must be absorbed to maintain a uniform drug level for a predetermined number of hours may be computed from the $t_{1/2}$ or k. For example, if it is established that 0.333 gm. of plain, fairly rapidly absorbed drug gives a peak response at a desirable but minimal level of activity, and the elimination constant k is $0.15^{-hr.}$ (15 per cent per hour), drug in the maintenance portion of the dose must be available for absorption at an approximate rate of 0.333 x 0.15, or 0.05 gm. per hour. The maintenance portion of the dose should begin releasing drug immediately after administration, according to this calculation.

Calculations may be extended to estimate what proportions of the dose should be in the quick-release and maintenance portions of the sustained-action dosage unit.[6, 9-12, 15] For a drug exhibiting the characteristics just described, one may compute

$$W_t = W_o + kW_oh \qquad (3)$$

where W_t is the total drug in dosage unit, W_o is the quick-release drug, and kW_oh is the maintenance portion.

Thus, if $W_o = 0.333$ gm., $k = 0.15^{-hr.}$, and $h = 10$ hours (the approximate duration of time during which sustained action at some level may be required), susbtitution of appropriate values in the equation gives

$$W_t = 0.33 + (0.15 \times 0.333 \times 10)$$
$$= 0.833 \text{ gm.}$$

The previous equation and calculation may be modified slightly when body drug content, absorption rate, and excretion data are known more completely or presented differently than given here.[6, 11, 15]

This information provides the product development pharmacist with a first estimate of a release design, which may be reasonably expected to approach the requirement of sustained action set forth for it. *In vitro* release tests and *in vivo* evaluation studies thereafter serve as further experimental guides to determine the release specifications of the final dosage form that will result in a therapeutically

efficient product. The *in vitro* tests are primarily valuable for control purposes; the *in vivo* studies in animals and ultimately in human subjects are of the greatest importance in determining what changes are necessary in the release design to assure a product of good utility under the conditions that it will be administered.

Release design variations as function of half-life. In comparing the half-lives of a number of sulfa drugs we may note that:

1. Biologic half-life varies with chemical structure. About a 17-fold difference in biologic half-life exists within a group of these listed compounds.

2. Minor changes in chemical structure may result in profound changes in half-life. There is a four fold difference between sulfaethidole and sulfamethylthiadiazole (SMTD), which differ structurally by only a methylene group.

3. A short-acting sulfa such as SMTD requires a far larger maintenance portion to keep initial blood concentrations at peak levels than is required for a sulfa with a larger biologic half-life. For a sulfa with a biologic half-life of 34 hours, for example, the peak blood concentrations do not subside sufficiently in 12 hours to justify further pharmaceutical formulation to prolong the blood levels.

The difference in release designs required for drugs differing in half-lives is illustrated with sulfaethidole and belladonna alkaloids, in Figure 3. The descending line with the sharpest slope represents activity versus time data for belladonna alkaloids ($t_{1/2}$ = 1 to 1.5 hours), whereas the other line represents SETD ($t_{1/2}$ = 8 hours). The half-life for belladonna alkaloids was estimated from salivary suppression studies in human subjects,[6] whereas the value for SETD was determined from blood concentrations.[7-10] In the design of effective sustained-release products of these drugs for q. 12 h. therapy, we find experimentally that a 1:1 ratio of quick release to maintenance portion is satisfactory for SETD.[11, 12] For belladonna alkaloids, about a 1:4 ratio has been shown to provide an effective sustained-action product.[13]

Interrelationships of $t_{1/2}$ and k determined by different test methods. For some drugs, there is evidence that the same values of the performance indices, $t_{1/2}$ and k, are obtained irrespective of whether these are determined from blood concentration or urinary excretion data.[8, 14] It is reasonable to assume that this relationship would hold true for some of the chemotherapeutic antinfective drugs such as the sulfonamides and antibiotics. With drugs that have a direct pharmacologic effect on the tissues, and where compensating mechanisms may exist in the body, the significance of $t_{1/2}$ and k as determined from blood or urine studies is less clear. Ideally, for pharmacodynamic drugs, one should measure the intensity of pharmacologic response as a function of time, and express $t_{1/2}$ and k in terms of these data. Some of our studies along these lines lead us to believe that in

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some instances the values of the performance indexes for a given drug may be different, depending upon whether these are determined from blood concentration or pharmacologic response studies.

Since therapeutic response is the important factor clinically, it is not difficult to rationalize that performance indexes for pharmacodynamic drugs might preferably be based upon pharmacologic data. Pharmacologic response studies have the advantage over blood concentration studies of reflecting the effect of the active metabolites in addition to the effect of the administered drug;[6] however, their use also has some disadvantages. Accurate measurements of intensity of pharmacologic response in terms of a useful therapeutic quality are difficult to make in human subjects, especially at the relatively low drug levels associated with therapeutic doses; nonetheless, work is being done in the development of pharmacologic response tests which may be applied to laboratory test animals and human subjects. At this time there is little doubt in my mind that for some drugs the performance indexes determined from pharmacologic responses will be very important in the objective approach to design and formulation of sustained-action products.

Preparation and Therapeutic Effectiveness

We have noted some of the important considerations that go into the selection of a drug for a sustained-action form, how the rate of disappearance of drug activity is a factor in the release characteristic a sustained-action product should possess, and some of the approaches to objective evaluation of drug and product performance. Now we might consider in further detail some of the steps in preparing and evaluating the sustained-action dosage form.

During and after formulation, the pharmacist must consider incompatibilities, chemical stability, shelf life, and the other usual problems associated with development of a product. In addition, with sustained-action products, *in vitro* release tests are run primarily to establish control specifications. Products having different durations of *in vitro* release are prepared, and then are made available for evaluation by *in vivo* methods. At this stage of formulation, past experience is valuable in estimating a reasonable *in vitro* release that might result in a useful *in vivo* performance. Tests of toxicity, safety, drug availability, and product efficacy are performed first on laboratory test animals, then on humans. The information acquired here is correlated with previously obtained information from studies of the plain drug in laboratory test animals and human subjects. A preliminary product design is finally supplied to clinical investigators for additional objective and subjective data which compares plain oral dosage forms with the sustained-action product. When an apparently satisfactory release and absorption occurs from the product, several clinical specialists will test the product subjectively on large groups of subjects whose

medical histories suggest that they give a normal response to medication. Finally, if the product performs satisfactorily, it is given to general practitioners for subjective tests on a considerably larger number of subjects. Care must be taken during each of these investigational steps to design studies that permit as precise and unbiased an evaluation of the product as possible. This may require the use of double blind, cross-over, paired-subject, or other statistically designed studies, depending on a number of factors, including the stage of the evaluation. All the data of objective and subjective studies are finally assessed and made available to cooperating physicians. The final and most important decision pertaining to efficacy of the product is based on the opinions of clinicians, who must determine that the product performs a useful therapeutic function, is safe for human use, and provides some advantages over existing medication.

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MAKING SUSTAINED-ACTION FORMS

(*Continued from page 467*)

keted for drugs[17] that are absorbed sublingually. Here the tablet may be held in the mouth until the outer coating containing the sublingual drug dissolves. The taste from a flavor coating between the sublingual and sustained-action portions is used to indicate complete removal of the sublingual portion and when the tablet should be swallowed.

Another manufacturer[17] uses a plastic matrix in a compressed tablet, which apparently has a high interstitial porosity. The drug is said to leech continuously from the tablet. How the amount of immediate release is controlled is not entirely clear, although this could be a function of porosity and surface area. Drug could also be coated onto the surface of the tablet proper. It is also not clear whether the inert matrix eventually disintegrates in the body, or is excreted as an intact core.

Liquid sustained-action preparations have also been marketed. The majority of these contain ion exchange resin salts or tannates. The patent held by Robinson and Svedres[18] is of the formulated type. Here, the drug is dispersed in a suitable matrix such

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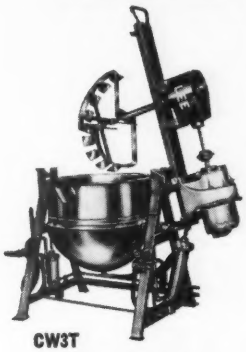

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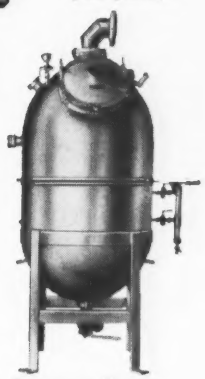

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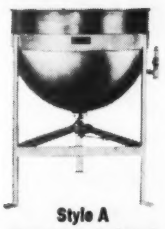

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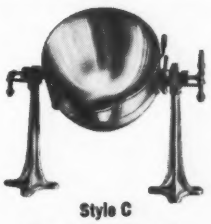

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as waxes, fatty alcohols, glycerides, silicone, polymers, and cellulose.

The resulting suspension is then spray-dried, spray-crystallized or dried, congealed, and pulverized to form the desired powder. An emulsification technique can also be used to prepare these particles as outlined in the patent held by Grass and Robinson.[19] Here, a drug of a particle size of less than 10 microns is mixed with a liquefied lipid material which is water insoluble and has a high melting point, normally about 85° C. The mixture is then solidified by cooling or drying, and comminuted to form a primary powder having a maximum particle size ranging from 5 to 25 microns. This primary powder is then suspended in a melt of a lipid material having a melting point substantially lower than that used in the primary powder. The molten mixture is then emulsified in water maintained at a temperature above the melting point of the second lipid and below the melting point of the first mentioned lipid material.

The emulsion containing the sustained-action particles prepared in this manner may be used per se, or after cooling, or the material may be allowed to separate and the sustained-action powder collected. Sustained-action powders obtained in this manner may then be suspended in a liquid vehicle. In this instance, of course, the drug must be relatively insoluble in the fluid in which it is to be suspended. The preparation of a liquid sustained-action form of sulfamethylthiadiazole and sulfaethidole have been described by Robinson et. al.[4, 20]

One may also obtain a prolongation of dissolution or sustained action by chemical means. A reduction in solubility of drug in gastrointestinal fluid normally will result in a more prolonged *in vivo* absorption. It is thus possible, through the synthesis of insoluble compounds, to obtain a type of sustained action. Although apparently not synthesized specifically for this purpose, both benzathine penicillin G and acetylsulfisoxazole show a significantly greater prolonged action than the more soluble potassium penicillin G and sulfisoxazole.

Medicament solubility may also be reduced by the formation of insoluble complexes. Cavallito[21] describes the preparation of insoluble tannic therapeutic amine complexes. A ratio of five parts of amine to one part of tannic acid is said to provide the least soluble compound. Commercially, according to Cavallito,[21] pectic or polygalacturonic acid is added to retard further the dissolution at the more acid *p*H values.

Amines may also be complexed with cationic exchange resins. Chaudhry and Saunders[22] describe the preparation and *in vitro* evaluation of the ephedrine complex of a sulfonated polystyrene resin. Brudney[23] describes the preparation of similar resin complexes with d-amphetamine, riboflavin, and penicillin V. Although there is no question that these complexes exhibit prolonged dissolution, especially in acidic

media, it is not entirely clear from published data how the *in vivo* dissolution rate can be controlled so that it will correspond reasonably well with drug disappearance or diminution of therapeutic effect following absorption of the quick-release portion of the dose. Brudney,[23] however, suggests that this is a function of the type of resin selected (sulfonic acid type being preferred), the particle size, degree of cross linkage, and treatment during complex formation. For example, he suggests acid washing to remove amphetamine from the surface of the particles.

Although the ion exchange resin complexes are often referred to as adsorbates, resins are usually not considered adsorbents in the classical sense. However, it is possible to prepare adsorbates using such materials as the bentonites or silicates, or charcoal. These adsorbates should release medicament slowly over time. To date, to the best of my knowledge, no product using this principle has been marketed, perhaps because drug is too tightly bound. The amount released with time from the adsorbate may then be too prolonged, with a resultant loss in physiological availability of the medicament.

Sustained-action forms prepared by chemical methods are commercially available as tablets, capsules, and aqueous suspensions.

These are some of the techniques which have found acceptance in the formulation of sustained-action products. Almost anyone with the information from the literature can formulate a product that will provide some prolongation of absorption. It is, however, imperative that all manufacturers do more than this to produce a reliable product. They must, as I noted earlier, set somewhat rigorous standards based on *in vivo* performance and *in vitro* control. These will include not only *in vivo* and *in vitro* testing techniques, but also suitable clinical studies. It must be ascertained without reasonable question that the product is efficiently absorbed and that therapeutic levels are maintained for the time periods claimed.

Of equivalent importance is the testing of the stability of our dosage form. Sustained-action dosage forms must be tested by the same standards employed to determine active ingredient stability. This will include storage at both normal and elevated temperatures, with the necessary extrapolations to insure that the product several years later will provide medication for absorption at the same rate as when originally formulated. This can include clinical evaluation of aged samples where indicated. Finally, having ascertained that the designed product will provide the desired clinical effect over the prescribed time period, that it is suitably stable, directions for manufacture and control procedures should be sufficient to eliminate variables such as lot-to-lot and dose-to-dose irregularities.

Although the methods of obtaining sustained action that I have discussed may not be in all instances ideal, more than eight years of use has shown that

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Sustained-release medication has been well-accepted by both physician and patient. As new techniques for testing and evaluation evolve, there will undoubtedly be an improvement of current methods, as well as the development of new methods.

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HAIR BLEACHES

(Continued from page 469)

suggests that the heavy metal content should not exceed 0.1 ppm. each, in water for this application. In deionization, practically all the dissolved salts are removed, while, in water softening, the salts are merely solubilized. Water softening procedures are not applicable in preparing dilute peroxide solutions.

Mixing equipment should be composed of either pure aluminum or glass. Agitators of stainless steel are preferable. Strict avoidance of contact with copper, lead, iron, brass, bronze, lubricating oils, and grease is necessary to prevent rapid decomposition. Peroxide manufacturers usually offer complete engineering information to those seriously interested in merchandising dilute peroxide solutions.

Regardless of the care exercised in manufacture, accidental contamination may occur. For this reason, stabilizers are invariably used. They would include:

1. Sodium stannate-tetrasodium pyrophosphate
2. Phenacetin
3. Acetanilide

Some objection has been raised regarding the use of acetanilid, because of the shoe polish odor and the discoloration that may result from the eventual oxidation of this compound. Nevertheless, this apparently has not prevented its widespread use. Small amounts of stabilizer are needed; in the case of phenacetin, for example, 400 mg. per liter of dilute peroxide will suffice.

When one pound of 35 per cent hydrogen peroxide is added to 4.9 pounds of deionized water, the resultant mixture will comprise theoretically, a 6 per cent solution of hydrogen peroxide, by weight. In manu-

facture, a portion of the water is used to dissolve the stabilizer. This is usually done with the aid of heat and agitation. The solution is then added to the water in the mixing tank, and the 35 per cent peroxide is fed in, with agitation. A 10 per cent solution of phosphoric (phenacetin or sodium stannate-tetrasodium pyrophosphate) or hydrochloric acid (acetanilide) is used to adjust the *p*H within a range of 3.5 to 4.0.

In packaging, clean, dust-free amber bottles are regularly used. The bottle caps should be lined with wax, vinyl or aluminum. Vented caps are recommended, but leakage may occur, particularly if the bottles are inverted in transit or storage.

The dilute peroxide may be assayed by titration with potassium permanganate, sodium thiosulfate, or ceric sulfate. In the presence of organic matter, the iodometric and ceric sulfate procedures are preferable. Shelf life may be predicted by means of accelerated, hot-storage stability, or other tests.

One useful procedure for predicting storage stability of dilute hydrogen peroxide is based on exposure to heat for 24 hours, under controlled conditions. A sample of peroxide solution is assayed and then placed in a specially cleaned flask and immersed in a 100° C. water bath for 24 hours. At the end of this period the solution is again assayed for hydrogen peroxide content. The stability value is calculated from the following formula:

$$\% \text{ Hot Stability} = \frac{\text{Final hydrogen peroxide concentration}}{\text{Initial hydrogen peroxide concentration}}$$

Peroxide solutions which record hot stability values over 90 per cent are believed to exhibit excellent stability during normal, room-temperature storage conditions.

In addition to the basic peroxide solutions, various modifications have appeared for the purpose of enhancing the appearance, performance, and handling convenience of hair bleaches. The so-called white henna preparations, which appeared years ago, were essentially magnesium carbonate-sodium perborate mixtures used in conjunction with ammonia water. An improved version covered by French patent involves: 20 parts ammonium persulfate, 15 parts magnesium carbonate, and 50 parts calcium carbonate, to which is added 15 parts sodium percarbonate.

To the combined mixture, 100 ml. of a solution containing 20 ml. of 12 per cent hydrogen peroxide and 80 ml. of water, is added.

The newer lotion bleaches and developers are often based on nonionic surfactants which, when properly employed, contribute to penetration. These lotions have a very pleasing appearance and vary from milky solutions to fairly heavy (but nevertheless flowable) creamy emulsions. They are exemplified by the following basic formulations:

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Hydrogen peroxide 35%	15.4%
Brij 30	2.0%
Brij 35	1.0%
Cetyl alcohol	1.0%
Stabilizer	q.s.
Acid for pH adjustment	q.s.
Deionized water, q.s. to make	100.0%

A different approach in a fairly recent French patent involves acid peroxide bleaching. While the product is not suitable for complete decolorization, it nevertheless is claimed to function as a useful hair lightener. A peroxide solution of a little under 5 per cent is acidified with an organic acid. Bleaching action is accelerated by means of cationics which serve as penetrants and conditioners.

Acid Bleaching Lotion

Hydrogen peroxide, 3%	97.1%
Alkyl ethyl morpholinium ethosulfate	1.5%
Adipic acid	0.8%
Sodium stannate (stabilizer)	0.6%
	100.0%

(pH 4.0 to 4.5)

Modern versions are, essentially, either oil or cream bleaches and, as in oxidation dye vehicles, are clear alkaline solutions. Oil bleaches usually require no pre-shampooing and are usually activated by combining one part of the base with two parts of 6 per cent hydrogen peroxide. After bleaching, the hair is rinsed with warm water and dried. Hair dyes are used in certain commercial products to provide gold, ash blonde, silver, and red tones during bleaching. In this particular application, the hair is shampooed on completion of the process.

The cream bleaches, when combined with peroxide, may either be shaken in an applicator bottle to produce a thin cream, or whipped to a thick consistency with a spoon, egg beater, or electric mixer. Bleaching action is stopped by rinsing with moderately warm water. In both the oil and cream bleaches, the use of conditioning and other agents helps minimize the adverse effect of rinsing with water or shampooing.

The oil and cream bleach compositions represent arcane formulations, but are roughly comparable to oxidation dye vehicles. It must be realized that bleaches may be kept on the hair for appreciably longer periods than oxidation dyes. Therefore, every precaution must be taken to assure a minimum of irritation, discomfort, and hair damage.

Two stable cream formulas provided in a French patent follow.

Pure glycol monostearate	20 g.
Igepon T (Antara Chemicals Div., General Aniline & Film Corp.)	2 g.
Neutral stabilized 60 volume peroxide	35 g.

Water	50 g.
Cholesterol	1 g.
Lecithin	0.1 g.

Add ammonia before use.

Sodium persulfate	15 g.
Magnesium peroxide	10 g.
Glycol oleate	65 g.
Emulphor (Antara)	15 g.

Cream is used with an equal part of peroxide.

Urea peroxide has been used, primarily in tablet form, in place of hydrogen peroxide. Aqueous solutions are acid in reaction and the *p*H of a 10 per cent solution is about 2.7. It is a relatively stable compound, particularly if kept free from metals such as iron and copper, which serve as catalysts. Heat and moisture will also reduce stability. The active oxygen content averages around 16 per cent. Certain oxidation dyes are packaged with urea peroxide tablets, which are crushed and added to the dye before use.

Persulfate salts, particularly ammonium and potassium, are utilized to accelerate or boost the bleaching action. Both are stable compounds, if handled properly. The active oxygen content of amminum persulfate is about 6.8 per cent, and it is very soluble in water (80 g./100 ml. water). The *p*H of a saturated aqueous solution is about 2.0.

Potassium persulfate has an active oxygen content of 6.0 per cent, but it is far less soluble in water (4.7 g./100 ml. water). The *p*H of a saturated aqueous solution is 5.4. Both the potassium and the ammonium persulfate compounds require avoidance of metal contamination and moisture pickup during packaging, if stability is to be assured. Common metals such as copper, magnesium, zinc, iron, and nickel react promptly with persulfates and deterioration is augmented in the presence of moisture.

PATENT THOUGHTS AND TRENDS

(*Continued from page 493*)

is afforded by the following claim taken from the patent.

"1. An orally administrable poliomyelitis virus vaccine comprising an aqueous attenuated non-pathogenic poliomyelitis virus suspension adsorbed by substantially non-hydrated gelatin particles from 10 to 140 mesh as water of hydration, the amount of gelatin being sufficient so that after hydration with the virus suspension, the particles are substantially dry, said virus vaccine being free-flowing, particulate, granular, and storage-stable with respect to its activity."

One can only hope that actual experience on a large scale will show that we now have the means to stamp out entirely the dreaded poliomyelitis, whether the ultimate answer is the Sabin, Cyanamid or another product.

(*Continued on page 570*)

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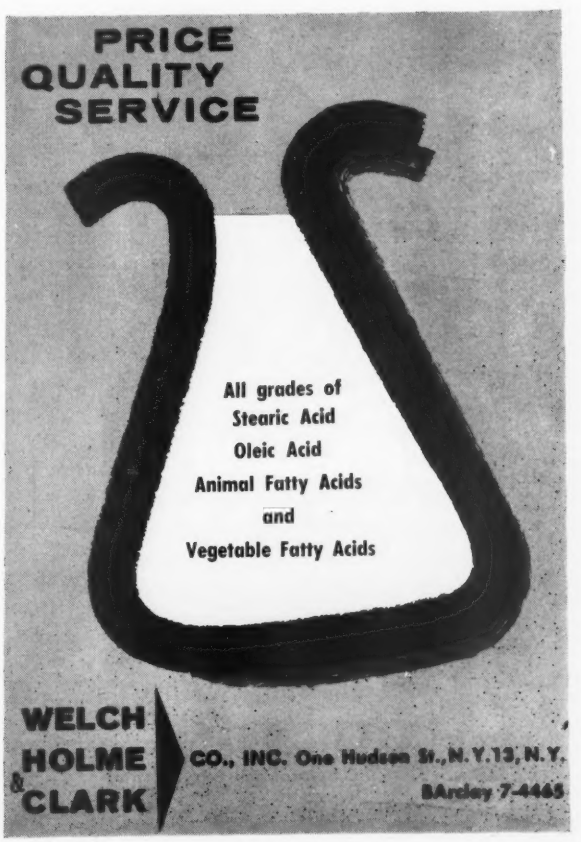

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(*Continued from page 471*)

price of milk is of far greater importance to the average family than a similar change in the price of tea. Weighting the items in an index serves the purpose of putting these price changes in their proper perspective.

The best known of all price indexes is the Consumer Price Index of the United States Bureau of Labor Statistics (B.L.S.), sometimes incorrectly referred to as the Cost of Living Index. This index tells us what is happening to the prices of the ordinary commodities and services we use in everyday living. It includes the prices of food, housing, house furnishings, clothing, medical care, transportation, personal care, reading and recreation, and a group of items that cannot properly be classified in any of the other categories. So great is the confidence in this index that some 4,000,000 unionized employees have their wages raised or lowered by the movements of this index.

And now, let us turn our attention to this new index, the Index of Wholesale Prices for Ethical Prescription Pharmaceuticals, which measures the changes in the prices paid by pharmacies for specialty drugs used in filling prescriptions. It measures changes in prices only. It tells us nothing about the changes in the kinds or amounts of drugs prescribed by physicians, the service charge imposed by some pharmacies, or the total amount of money spent for drugs. Because these changes do take place, it is the statistician's duty to adjust for these factors in constructing the index. If this were not done, we would get into the realm of drug costs.

This index is an annual index, that is, prices are measured once a year, covering the period from 1949 through 1959.

To construct this index involved the development of answers to a series of questions, the most important of which were:

1. What drugs should be included in this index?
2. How should the drugs be classified?
3. Where should the data on prices and importance be obtained?
4. How many drugs should be included in each group in our classification scheme to get adequate representation of importance and price movements?
5. What is the relative importance of each drug within a group and of the groups to each other?
6. What should be done about keeping the list of drugs current and realistic, so that drugs which have disappeared almost completely are excluded from the index, while at the same time the new drugs, as they appear on the market, are introduced into the index?
7. What base period should be used?
8. And last, there are the many technical problems involved in constructing this index.

The available data were studied and, after expert consultation, it was decided to classify drugs according to their therapeutic use in new specialty prescriptions.

The categories agreed upon were these:

	Percentage Share of New Specialty Prescriptions	
	1949	1959
1. Vitamins	13	4
2. Hormones	10	11
3. Antibiotics—oral	11	23
4. Sedatives—hypnotics	6	3
5. Analgesics—narcotics	4	7
6. Cardiovascular agents	4	4
7. Diuretics	0	3
8. Hematinics	4	2
9. Antihistamines—oral	5	2
10. Dermatologicals	4	3
11. Sulfonamides	3	4
12. Antispasmodics	4	5
13. Central Nervous System stimulants	4	2
14. Cough and cold products	6	5
15. Tranquilizers	0	9
16. Antiarthritics—antirheumatics	1	1
17. All others	21	12

The sixteen therapeutic groups, in recent years, alone account for more than 80 per cent of the dollar volume of new prescriptions written. In 1958 the indexed specialties accounted for no less than 30 per cent of all specialties in the vitamin-nutrient group, and up to 85 per cent in the antiarthritic-antirheumatic group. When a drug might properly be classified in more than one category, it was classified according to its most important application.

Changes in drug usage have changed the relative importance of these groups. In 1949, the three most important groups were vitamins, antibiotics, and hormones. They accounted for 12.9, 10.8 and 10.4 per cent, respectively, of consumer dollar expenditures for all new prescriptions for ethical pharmaceutical specialties. In 1959, the three most important groups were antibiotics, hormones, and tranquilizers. The contribution of these groups was 23.3, 10.8, and 8.7 per cent, respectively. Antibiotics more than doubled in importance. Hormones remained virtually unchanged. Vitamins, most important in 1949, declined to ninth place in the 16 therapeutic groups. Tranquilizers, unknown in 1949, have become the third most important group.

The data on both prices and sales volume, which were used to determine importance, were derived from Drug Topics Red Book, and represent the prices prevailing at the time it went to press in each year.

To assure adequate coverage in each group, the five specialties that led in dollar volume in each of the 11 years were listed. If the item appeared in any year, it was included in the index for as long as it appeared on the market. For each specialty, the most important dosage form is used to represent the prices of all the dosage forms for that specialty. For many specialties only one dosage form exists. Where divergent price movements for different dosage forms were noted, a sufficient variety of dosage forms to portray adequately the price movements of the specialty is used. Thus, a total of 308 specialties appears at one time or another. Of these 308, 99 or less than 1/3 were in existence in 1949, 66 have virtually disap-

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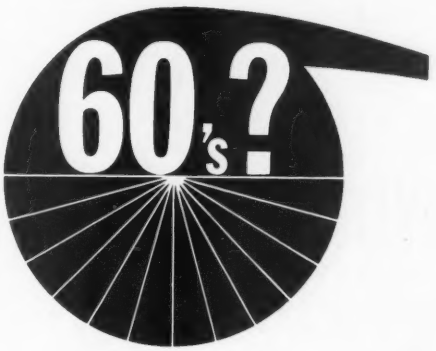

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peared from the market, and only about one-fifth, or 68, have existed continuously. The 1959 index is based on 242 items.

The base period for the index is 1949, the first year for which data are available. This base is the closest to the 1947-1949 base used in the Government price indexes. Thus, comparisons with Government indexes can be made most readily.

The method of index computation is known as a chain index of weighted price relatives. This technique provides the flexibility necessary to change weights as often as may be necessary—in this index the weights are changed every year—and to introduce new drugs when they become of sufficient importance for inclusion in the index, and at the same time to permit the dropping of items when they decline in importance or disappear from the market, without invalidating the comparability of the index over time.

Now, this Index of Wholesale Prices for Ethical Prescription Pharmaceuticals shows that wholesale prices have declined more than 7 per cent since 1949. This contrasts with the 20 per cent increase in all wholesale prices as measured by the B.L.S. Index of Wholesale Prices. If farm products and foods are excluded, the rise in wholesale prices is 27 per cent. In this same period, consumer prices have risen 22 per cent. A subgroup of the B.L.S. Wholesale Price Index is called "drugs and pharmaceuticals." This consists of 40 ethical and proprietary drugs and pharmaceuticals, including such items as citric acid, agar, ethyl alcohol, chloroform, cod liver oil, glycerine, gum arabic, iodine, menthol, penicillin, sulfadiazine, and vitamins B_1, B_2, C, and D. The B.L.S. subgroup does not include any cortical steroids, tranquilizers, broad-spectrum antibiotics, or the newer forms of vitamin products. The majority of the items in the B.L.S. index are long-standing basic ingredients, particularly for proprietary drugs, but they are an inadequate reflection of today's prescription market. However, even for this less representative list of drugs and pharmaceuticals, prices in this period of time have declined 0.2 per cent. The prescription and drug component of the Consumer Price Index, that is, retail prices for drugs, has risen nearly 20 per cent since 1949, somewhat less than the rise in all retail prices; however, it consists of the following six items: three prescription items—APC tablets, elixir terpin hydrate with codeine, and buffered penicillin —and three nonprescription items—aspirin tablets, milk of magnesia, and vitamins. That is all—a woefully inadequate and unrepresentative list. This Consumer Price Index is now being revised and expanded to 18 items to include items from eight of the 16 groups in our index. While this is a considerable improvement, it is still too small to represent the retail drug market adequately. But, before hastening to point an accusing finger at the Bureau of Labor Statistics, it must be borne in mind that drugs con-

stitute less than one per cent of consumer expenditures. The Bureau with its limited funds cannot afford to spend additional money for broadened coverage of this group without seriously impairing the quality of the over-all index. As a result of the current revision of the drug group, 6 per cent of the items in the index will be drug products, yet this component is less than 1 per cent of total consumer expenditures.

It is eminently apparent that, while the Government indexes in this area are adequate for the role they play in measuring the course of all prices in this country, they cannot serve as satisfactory measures for this industry.

Since 1949, our index shows that the sharpest price declines were in the two most important groups. Antibiotics, which constitute in value nearly 25 per cent of all new ethical prescription pharmaceuticals, have declined more than 50 per cent in price. Hormones, which have an importance of more than one-tenth of all pharmaceuticals, declined 40 per cent in price. The remaining groups showed smaller changes —some up, some down. Drug prices declined 4 per cent between 1949 and 1950, 3 per cent between 1951 and 1952, and 1 per cent between 1953 and 1954. Between 1956 and 1957, there was a 1 per cent rise. Since 1952, drug prices have remained quite stable. In this same period of time, according to the Bureau of Labor Statistics, all commodities, other than farm products and foods, rose 13.5 per cent; chemicals 5.3 per cent; and drugs and pharmaceuticals, 1.3 per cent. This discrepancy between our index, which has remained stable, and the Government index, which shows a rise of 1.3 per cent, small as it is, is largely due to the absence from the B.L.S. index of the newer drug products, such as corticosteroids, which have declined in price since 1952.

Much has been said about the high price of drugs. Senator Kefauver in his speech of March 22, 1960, in the Senate on administered prices stated: "To a large proportion of the elderly people, many of whom live on small, fixed incomes, the price of drugs constitutes something of an economic crisis." Later in this speech he accepted the statement of Senator McNamara that the average person over 65 spends $42 per year for drugs and medication. Senator McNamara went on to add that "three out of every five people over the age of 65 in this country have a money income of less than $1,000 per year." To which Senator Kefauver replied that this "emphasizes the reason why the older people have a very hard time obtaining the high-priced drugs which they need so badly." Is not the problem of the elderly, then, the inflation, not of drugs, which have declined in price, but of food, housing, and medical care other than drugs, which has reduced to less than half the purchasing power of what should have been an adequate income? It is ironic that the increase in the number of older people in our country is primarily due to the new life-saving drugs. The very

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industry that has contributed so much to the prolongation of life is now being held responsible for the economic plight of those whose lives it has helped to preserve. Mandatory retirement rules and Social Security restrictions on earnings prevent these people from earning their living, and make it necessary for their meager savings to be stretched over a longer retirement period. There is no doubt that, even if these elderly people received their drugs free of any charge, their economic difficulties would not be solved. The solution to the problem lies in restoring the purchasing power of the fixed incomes of our pensioners. If this is to be achieved by rolling back prices—I do not advocate this—then all prices should be rolled back, a well-nigh impossible task.

The pharmaceutical industry should develop its own authoritative analyses of prices at the wholesale and retail level in order to understand and to show more fully to the nation what really is happening; to show how successful this industry has been in controlling price inflation. There is today no adequate measure of retail drug prices. These is no measure of what has happened to the prices consumers pay for their prescriptions. Again, please note that I am not referring to his expenditures for drugs, but to the prices he pays for his pharmaceutical drug prescriptions. Careful studies should also be made of the costs of production, the productivity of the industry, and the costs of distribution and obsolescence rates, so that sensitive indicators of changes in costs are more quickly available, in order to maintain equitable pricing. The pharmaceutical industry may well be proud of its record, but it should develop the statistics needed to interpret that record.

LIBRIUM

(*Continued from page 461*)

This advertising copy, written by John Kallir of the McAdams agency, served as the prelude to the major sales points to be made for Librium. It anticipated the questions and objections likely to be raised by doctors, and by so doing robbed them of much of their skepticism.

There was, of course, nothing "relaxed" about the promotional points made after this introductory statement. It was hard-sell all the way. Side-by-side diagrams plotted the effect of Librium on monkeys and the comparable effects of meprobamate and chlorpromazine: These showed that Librium had the most dramatic effect in reducing aggression and the least effect on normal activity. From one of the 17 papers published on Librium, the ads pulled this statement for use as a theme line: "Librium is as different from the tranquilizers as they were from the barbiturates."

As the campaign unfolded and more and more doctors began to prescribe Librium, Roche continued to hammer away at the uniqueness of the drug. Case histories were reported to show how Librium had worked where previous tranquilizers had failed. The rapid acceptance of the drug by doctors led Roche very early in the game to identify Librium as "the successor to the tranquilizers"—"successor in scope," "successor in safety," and "successor in effect." As a measure of Librium's impact, consider this: How many new drugs can claim to have made previous agents obsolete after only three months on the market?

The rise of Librium in the market can be shown in national audits of new prescriptions. (See table, page 461.) In January, before its introduction, the tranquilizer field shaped up like this: Equanil, Compazine, Thorazine, Miltown, and Stelazine—the top five brands—accounted for 70 per cent of the market. The gap between them and the rest of the field was considerable. Atarax, a drug marketed by the J. B. Roerig division of Chas. Pfizer & Co., held sixth place with 67,000 new prescriptions in January—only a little more than half of Stelazine's total.

In March, Librium's first month on the market, the audit of new prescriptions filled showed a changing picture. Already, the Roche product was beginning to chip away at the market franchises held by the leaders. Atarax prescriptions dropped during March to 43,000.

In April, Librium really begins to move. It edged ahead of Equanil in May, and the June figures showed Librium at the top with 325,000 new prescriptions.

Once in front, Librium has not stopped. It has since lengthened its lead, and is now approaching a market share of 20 per cent—the runaway ethical of 1960. It should be pointed out, however, that the audit figures above understate the volume done by SK&F's Thorazine, a potent drug widely used in hospitals. This institutional use is not always reflected in audits of new prescriptions. Even so, there is no doubt that Librium has become the most widely used tranquilizer in general practice. Surveys taken after the drug was on the market only three months indicated that three out of ten doctors had already prescribed it.

One product caught in the Librium blitzkrieg was Striatran, a tranquilizer launched by Merck, Sharpe & Dohme in August. Striatran is a "manipulated molecule," that is, it is related to the meprobamate family. It featured two improvements over the meprobamates: (1) it is "effective in half the dosage required with meprobamate;" and (2) it produces "much less drowsiness" in patients than the meprobamates. With advantages such as these, Striatran had the potential of becoming a major new volume producer for Merck—had Librium not appeared on the scene. With Librium sweeping everything before it, Striatran has a strictly limited market potential. Timing is of crucial importance in ethical drug marketing.

One thing Librium has *not* done is to expand the total tranquilizer market. New tranquilizer prescriptions have remained fairly stable at about 1,500,000 a month—before and after Librium's introduction. What Librium has done is to redistribute radically the market shares. In building its own business, it has gouged deeply into the markets of both the phenothiazines and the meprobamates. The figures above show this action clearly. From their highs in January, Equanil was off 25 per cent by June, Compazine, 40 per cent, Thorazine 33 per cent, and Miltown 20 per cent. Only SK&F's Stelazine has held its own.

In other words, Librium's strategy of aiming at both halves of the market has paid off handsomely for Hoffmann-La Roche.

ANTI-STAPH PENICILLIN

(*Continued from page 528*)

lar administration of penicillin x-1497 at 200 and 500 mg./kg., for 10 and 6½ weeks respectively, without obvious toxicity. Rats maintained normal growth rates while receiving 200 mg./kg. (I.P.) daily for 12 weeks. Intravenous administration of 300 mg./kg. per day for three weeks was not accompanied by demonstrable toxic effect in dogs.

The absorption, excretion, and distribution of penicillin x-1497 have been studied by *G. A. Cronk*, using healthy adult volunteers. Following the oral administration of 1000 mg. of penicillin x-1497 in aqueous solution, penicillin could not be identified in the serum. Single intramuscular injections produced average penicillin serum concentrations at 15 minutes ranging from 2.6 to 7.3 mcg./ml.; at 30 minutes from 3.1 to 10.7; at one hour from 2.7 to 13.8; at two hours from 1.1 to 8.6; at four hours from 0 to 1.9. Following the intravenous administration of single doses of penicillin x-1497, the average penicillin serum concentrations at 5 minutes ranged from 11.8 to 109.2 mcg./ml. Following these initial high levels, there was a rapid penicillin runoff so that the average serum concentrations at two hours ranged from 0.1 to 4.8 mcg./ml.

Penicillin x-1497 is rapidly excreted in the urine, with 31 to 58 per cent of the I.V. dose, and 25 to 82 per cent of the I.M. dose being recovered in the 12-hour period after injection.

In a limited study of the distribution of penicillin x-1497 in the body after injection, none was found in saliva, cerebrospinal fluid, or stool. Excellent concentrations were found in prostatic fluid.

Experiments were conducted by *E. M. Yow, J. Reddin and W. Ure* in which staphylococcal abscesses are produced in rabbits by the subcutaneous injection of 5 ml. of a human blood containing staphylococci in a concentration of 5 x 10^6 bacteria per ml. Strains of staphylococci are used which are penicillin G-resistant and penicillin G-sensitive. All of the

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strains tested thus far in this laboratory have been sensitive to penicillin x-1497 *in vitro* in a concentration of about 3.12 units/ml. The results thus far indicate that penicillin x-1497 is active against infections due to penicillin G-resistant strains where penicillin G is ineffective. Where penicillin x-1497 has been used in the treatment of infection due to penicillin G-sensitive strains, the effective dose of penicillin x-1497 is greater than penicillin G.

Consecutively isolated penicillin G-resistant hospital strains of staphylococci from patients with active infections were tested against penicillin x-1497 by *I. M. Smith and G. W. Counts.* Bacteriostatic and bactericidal levels of penicillin x-1497 were compared to those of kanamycin, ristocetin, chloramphenicol, vancomycin, and penicillin G. Findings indicate that penicillin x-1497 is an excellent antibiotic for penicillin G-resistant staphylococci, followed closely by vancomycin, when *in vitro* tests are used as the criteria for choice.

Six cases of coagulase-positive staphylococcal infections sensitive to x-1497 were reported by *A. Branch, K. C. Rodger, and E. E. Power.* In one case, the drug was used topically as well as systemically.

In laboratory studies, no staphylococci resistant or sensitive to other penicillins, were found resistant to penicillin x-1497; four of the cases treated were resistant to penicillin G.

Blood level and urine assays were made, showing rapid absorption. The peak level occurred at one hour, with moderately rapid excretion, but therapeutic levels still remained in four to six hours.

Clinical response was good in five cases and only temporary in one. Improvement usually occurred within 24 hours of onset of administration of penicillin x-1497.

No significant toxicity was encountred, and local pain and irritation at the site of injection were absent.

Penicillin x-1497 was effective in the control of staphylococcal infections. One hundred strains of hemolytic coagulase-positive staphylococci were tested by *A. M. Rutenburg, H. L. Greenberg, and F. B. Schweinburg* for *in vitro* sensitivity to penicillin x-1497 and pencillin G. Ninety-eight strains, 95 of which were resistant *in vitro* to penicillin G were inhibited by 6.3 mcg./ml. or less of penicillin x-1497.

Thirty-five consecutive patients with infections due largely to pencillin G-resistant staphylococci, 26 of whom had failed to respond to this antibiotic, received penicillin x-1497. These included infection of postoperative wounds, soft tissue, respiratory and gastrointestinal tract infections. All 35 responded favorably to penicillin x-1497 therapy.

The drug was well tolerated, and no side effects were observed in this series of patients.

In vitro studies of x-1497 were carried out by *W. M. M. Kirby, C. E. Roberts, Jr., and J. D. Allen* to assess deterioration, bacteriostatic and bactericidal activity, resistance to destruction by penicillinase, development of bacterial resistance, and lytic action against staphylococci. In addition, pharmacological studies were performed in volunteers and in patients, and clinical efficacy was evaluated in a limited number of cases.

Preliminary results of these studies show that stability in tryptose phosphate broth at 37° C. was at least as great as that of penicillin G. In vitro activity of penicillin x-1497 against pneumococci and group A streptococci was one-third to one-tenth that of penicillin G. However, 50 strains of coagulase-positive staphylococci highly resistant to penicillin all showed minimal inhibitory concentrations of penicillin x-1497 of 5 mcg./ml. or less. In addition, the rate of killing of a penicillin-sensitive phage type 80/81 staphylococcus was comparable to that with penicillin G, and with a penicillin-resistant staphylococcus it was equivalent to that with vancomycin. The lytic action of penicillin G in low concentrations against sensitive staphylococci could be reproduced with low concentrations of penicillin x-1497 against both penicillin-sensitive and resistant staphylococci.

Fifteen patients were treated with penicillin x-1497. Highly favorable results were obtained in cases of pneumococcal pneumonia and in one case of acute osteomyelitis due to a penicillin-resistant staphylococcus. No significant side effects were observed in any of the cases.

Clinical experience with penicillin x-1497 by *W. L. Hewitt et al.* has consisted of the management of 43 patients primarily with staphylococcal infections.

Chemotherapy consisted of 4 to 8 grams daily by the intermittent intravenous route administering 2.0 grams every 6 hours, or the intermittent intramuscular route administering 1.0 to 2.0 grams every 6 hours. The duration of treatment varied from 6 hours to 43 days.

Seven patients with *Staphylococcus aureus* bacteriuria were treated. Staphylococci were eradicated from the urine in all instances during and after treatment and, in addition, bacteremia was controlled in the one instance in which it accompanied acute pyelonephritis. Thirteen soft tissue infections were treated. With concomitant surgical drainage in 11 patients, good clinical response occurred in all. All but one wound showed disappearance of staphylococci, although they reappeared after stopping chemotherapy in 3 instances. Treatment of 11 cases of staphylococcal osteomyelitis was followed by cure after short-term follow-up in 8 instances, and one failure in the presence of large sequestra which could not be removed short of amputation. One patient expired with *Proteus mirabilis* sepsis after 5 days of treatment with penicillin x-1497. One patient relapsed after discontinuance of treatment. Three cases of endocarditis were observed. *Streptococcus viridans* was the offending organism in two instances and *Staphylococcus aureus* in one. Dramatic clinical and

bacteriologic response occurred following institution of antibacterial therapy. Six acute pulmonary infections were treated. *Staphylococcus aureus* appeared to be the responsible organism in five individuals, one of whom had multiple lung abscesses and another an empyema. *Diplococcus pneumoniae* was the causative organism in the sixth patient. Excellent clinical and bacteriologic responses with disappearance of gram-positive cocci from the sputum occurred in all patients. Infections of the central nervous system occurred in three cases. Two occurred post-operatively, one being due to *Clostridium perfringens* and the other to *Staphylococcus aureus*. Adequate clinical response occurred in both these patients with sterilization of the drainage from the cranial cavity. A patient with pneumococcal meningitis expired six hours after the first dose of penicillin x-1497. The spinal fluid penicillin concentration was 11 mcg./ml., but the duration of treatment was inadequate for evaluating the effectiveness of any therapeutic agent.

In spite of abundant growth of *Staphylococcus aureus* from exudate on plates containing potassium penicillin G, and to a lesser extent on plates containing potassium phenethicillin, the preparation of over 90 cultures before, during and after treatment failed to show growth of a single staphylococcal colony on plates containing penicillin x-1497.

No major drug toxicity was observed and no minor evidences of hypersensitivity occurred. Thrombophlebitis and pain on intramuscular injection were extremely minor problems. Three patients gave a history of hypersensitivity to penicillin G but received penicillin x-1497 for periods of more than 28 days without side effects. In one of the cases with subacute bacterial endocarditis, an anaphylactic type of reaction to potassium penicillin G occurred 24 hours prior to institution of penicillin x-1497, which proceeded uneventfully over a 28-day period.

Treatment of a small group of patients with serious staphylococcal infections by *A. C. White and D. T. Varga* was highly effective in patients without serious underlying disorders, but the mortality remained high in patients with uremia, carcinoma, or other potentially fatal diseases.

The only toxicities encountered in this study were skin rashes in two of 40 patients who received penicillin x-1497 for any reason, and moderate pain at the sites of injection.

Penicillin x-1497 was employed by *V. Knight and D. Rifkind* in the treatment of eight cases of staphylococcal and two cases of streptococcal infections hospitalized at the National Institutes of Health.

Doses of penicillin x-1497 up to 15 grams daily were given intramuscularly or intravenously for as long as 48 days. Probenecid was found to elevate and prolong the blood concentrations of the antibiotic.

Clinical results were uniformly satisfactory. Infections caused by either penicillin G-sensitive or re-

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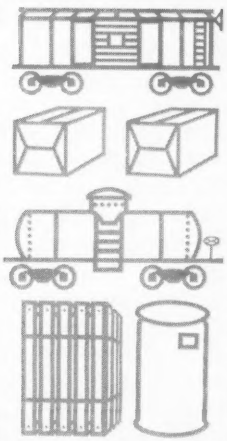

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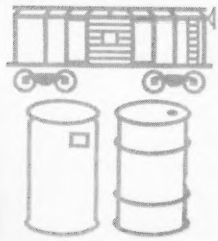

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sistant staphylococci were found to respond equally well to penicillin x-1497. No toxic manifestations attributable to this antibiotic were observed.

The report by *P. A. Bunn, R. Knight, and J. Amberg* is concerned with four aspects of the new synthetic penicillin, x-1497: its pharmacological properties in the human; an *in vitro* study of various materials to dilute serum containing it; some notes about the influence of penicillinase upon its antistaphylococcal activity; and a summary of its use alone in 25 patients with acute infections, most of them staphylococcal.

There is rapid attainment of peak concentrations in blood within one hour of a parenteral dose. Distribution into kidney, in cord blood, in peritoneal, pleural, and knee fluids is of the same order as that in blood. There is an appreciable blood brain barrier. Excretion is rapid through the urine; between one-third and one-half of a dose is recovered, most within eight hours.

In assaying penicillin x-1497 in blood, the cylinder cup plate method using *Sarcina lutea* is accurate and dependable, if normal serum or 1.75 per cent bovine albumen is used as the diluent.

When extracellular penicillinase is added to a medium containing penicillin x-1497 and actively growing staphylococci, it does not interfere with the antistaphylococcal activity of penicillin x-1497.

Twenty-two of 25 patients studied had staphylococcal disease of serious order. Three patients with pneumococcal pneumonia were also treated. The clinical and bacteriological responses were gratifying in all. Dosage used ranged between five and ten grams daily given parenterally. Therapy in the majority was continued for less than 14 days.

No patient demonstrated overt toxicity to penicillin x-1497. One of the patients treated was known to be hypersensitive to penicillin G and indeed had had a recent and serious skin rash from its use. This patient received 40 grams of penicillin x-1497 in a period of one week without untoward event.

Studies by *P. A. Day et al.* include both prophylactic and therapeutic trials with penicillin x-1497. These have been designed to evaluate further the role of this extremely promising new antibiotic on a pediatric service.

The prophylactic effect of this new penicillin against implantation of nursery strains of staphylococci was tested in the newborn nursery of two Syracuse hospitals. Study infants received a single 125 or 250 mg. injection of penicillin x-1497 within the first 24 hours of life.

Following a single dose of 125 mg., only 4 of 47 (8.5 per cent) infants yielded coagulase-positive staphylococci, while 17 of 49 (37.9 per cent) control infants were positive on cultures from either cord or nares. Three of the 4 cultures of staphylococci from injected infants were resistant to penicillin G, while 12 of the 17 from controls were similarly resistant. While these data suggest that this new antibiotic may be useful in the prevention of staphylococcal implantation under certain special conditions, it is clear that the duration of protection following a single dose is limited.

In a series of nine serious staphylococcal infections in infants and children, the therapeutic response was excellent in all but one case (where relapse occurred), regardless of the *in vitro* sensitivity of the organism to penicillin G.

No systemic reactions were observed and no evidence of induration or tenderness at the site of injection was noted, although single injections as large as 1300 mg. have been given.

S. Katz and J. Fedorho reported their laboratory studies of penicillin x-1497 concerning activity against staphylococci, penicillinase, and phage typing.

PATENTS

(*Continued from page 561*)

Brylcreem Ruled Infringed by Valcream

One of the main reasons that these columns have not carried many articles in the field of trademarks is the difficulty of trying to reconcile the various decisions for the readers. This is due to two main causes: (1) the well-known fact that trademark cases do not lend themselves very well to exemplification, for each case is really peculiar unto itself, and (2) this is not a legal publication and discussions in these columns are limited primarily to the factual information, rather than to a consideration of the legal issues involved. One result of the last point is that interesting trademark cases from the legal point of view are not even mentioned here if they do not deal with drugs, cosmetics, or allied materials.

A recent and important case which is believed to contain information of general interest and which is an excellent example of the danger of attempting to draw too many distinctions in trademark cases is one involving "Brylcreem" and "Valcream." In that case, the U. S. Court of Appeals for the Second Circuit (New York) ruled in a 2 to 1 decision that "Valcream" infringes "Brylcreem."

Facts. It appears that in the beginning of 1942 Harold F. Ritchie, Inc., a New Jersey corporation, and its predecessors in title sold the "Brylcreem" product in the U. S. and Canada, and in recent years Ritchie has been the acknowledged leader in the sale of men's cream-style hair dressing packaged in tubes contained in paperboard cartons. Ritchie has spent very large sums in advertising, its share in the U. S. market having increased from 2.6 per cent in 1953 to 11.9 per cent in 1958. In 1955, Chesebrough-Pond's, Inc., decided to manufacture and sell on the U. S. market a men's cream hair dressing in tubes. This decision was due to the increasing popularity of this type of product, and was made after a thor-

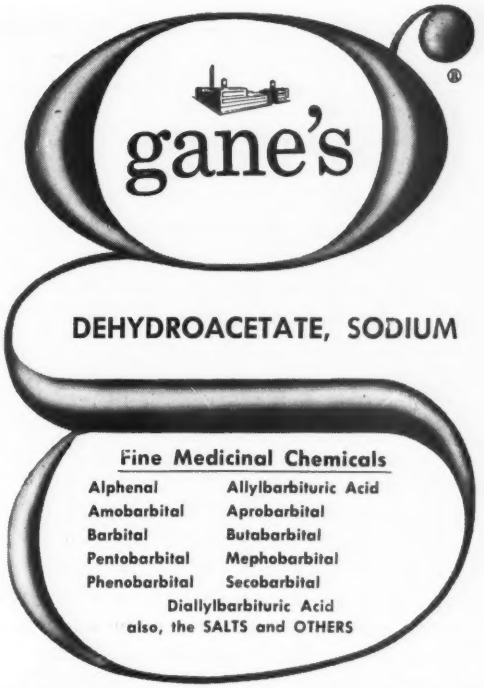
ough study of the new market created by "Brylcreem."

It appears that the two products are identical in the size and shape of the tubes and cartons, the prices are identical, the colors similar, the orifice is identical in size, and the advertising on the tubes and packages is substantially the same. All over, according to the court's opinion, the tubes are indistinguishable. They look, feel, and smell the same; and their ingredients are said to be virtually identical.

The majority opinion states that, once Chesebrough-Pond's decided to market a cream-style hair dressing in tubes, it asked the advertising agency to suggest names for this hairdressing "of the Brylcreem type," emphasizing that need for a name was of "top priority." The agency responded with a list of 25 names for "Bryl Cream type." From this list, Chesebrough-Pond's picked Valcream, one of the two names on the list which most closely approximated Ritchie's trademark.

A memorandum in November 1955 from Chesebrough-Pond's file reveals that the successful market "pioneering" by "Brylcreem" was a compelling reason for its choice of the name "Valcream." The similarities between the original Brylcreem tube and the Valcream tube are accounted for by the fact that when the artist was summoned to design the Valcream tube, there was a tube of Brylcreem on the desk in front of him. When it came to devising the instructions for use and the statement of ingredients on the outside of the Chesebrough-Pond's carton, the advertising agency was sent a carton of "Brylcreem" as an aid in composing a "like panel on Valcream." Even the color of the cap was made red, conforming with Brylcreem, when the question arose whether to make it red or white. Before marketing Valcream, Chesebrough-Pond's ran a series of "blind product tests" by which it was learned that "34 per cent . . . saw no difference between Brylcreem and Valcream. . . ." While the sample was too small to be definitive in preferences this close, it would appear, at most, that any superiority of Brylcreem would probably be no more than 1 percentile point over Valcream, if any.

The majority also felt that there was some evidence of actual confusion in the minds of the purchasers of these new products. It seems that Chesebrough-Pond's had made an offer by television in certain West Coast cities to make refunds to purchasers of the 59-cent size of "Valcream" by sending a check for the sum, signed by the well-known baseball player, Gil Hodges. It appears that there were 13 instances in which "Brylcreem" cartons were mailed to Ritchie in response to the Chesebrough-Pond's commercial. Chesebrough-Pond's also received at least ten, and probably more, Brylcreem cartons in response to its offer. There was no evidence of the receipt of cartons of any other competing hair dressing. There was some testimony of actual confusion by the department manager in charge of cos-



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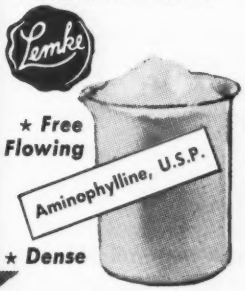

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metics in the Katz Drug Store in Des Moines, Iowa, and two employees of this company in Kansas City, Missouri, as well as a couple of other instances of actual confusion.

Majority opinion. The majority of two judges, whose opinion constituted the ruling of the court, took a very broad view as regards the rights of the first comer and the obligations of a second comer in the market place. It stated the rule that the second comer has a duty to so name and dress his product as to avoid all likelihood of consumers confusing it with a product of the first comer, quoting the following with approval:

"One entering a field of endeavor already occupied by another should, in the selection of a trade name or trademark, keep far enough away to avoid all possible confusion."

While recognizing that it is permissible in the American economy for the second comer to endeavor to capture as much of the first comer's market as he can, the majority stressed that the late comer must do this by giving his product a name and dress descriptive and fanciful in its own right and selling it on its own merit, not by confusing the public into mistakenly purchasing his product for his competitor's. The second comer must create a reputation of its own and not trade on the good will of another product already established at considerable cost and risk.

The majority opinion, noting what it termed the cumulative absence of differentiation, ruled that this was objective evidence of concious imitation. By absence of differentiation, the court meant that the products were identical in size and shape of tubes and cartons, the prices identical, the colors similar, the orifice identical in size, and the advertising on tubes and packages substantially the same, etc.

Further, the majority view was that the subjective evidence was of even greater significance than the objective evidence in showing actual intent to imitate. The court was led to this conclusion by the activities of Chesebrough-Pond's, already noted above in asking the advertising agencies to suggest names "of the Brylcreem type," having the Brylcreem tube before the artist who designed the Valcream tube, etc., etc.

The two prevailing judges felt that the question of whether "Valcream" and "'Brylcreem" were confusingly similar must be considered in conjunction with the similarity of the presentation of the product in respect to the design and general appearance, containers, tubes, price, size, perfume, and other nonfunctional aspects, and not merely by comparing the actual words alone. On this basis, the majority ruled in favor of Brylcreem.

In a very strong dissent, one of the three judges accused the majority of ignoring a number of cases where the Second Court of Appeals had refused to extend the trademark monopoly to prohibit the competitive use of a well-known and ordinary English word. The principal point made by the dissenting judge was that, since the suffixes "creem" and "cream" involved the use of a word that describes the product as well as a corrupted form of that word, and the prefix "Val" is wholly unlike the combination "Bryl," no basis for infringement could be found.

Readers of this column will recall the "Pepto-Bismol" vs. "Pepsomar" litigation. In that case, which bears some striking similarity to the present case, the lower court had ruled that there was infringement, but the upper court, that is, the same court which decided the "Brylcreem" case, ruled otherwise. In other words, the "Brylcreem" decision seems to be contrary to the "Pepto-Bismol" decision. Perhaps the more liberal (from the point of view of the trademark owner) "Brylcreem" decision represents a broadening of the attitudes of the court on this question and that later cases will follow its lead.

However, it is quite risky to draw such a conclusion. In this connection, for example, it is interesting to note that Prof. Walter J. Derenberg, perhaps the outstanding authority on the U. S. Trademark Act of 1946, in his 13th annual report on the administration of this act prepared for the American Bar Association, speaks of the great retrogressive trend of the second circuit decisions, citing the "Pepto-Bismol" case as an example. By retrogressive trend, Professor Derenberg referred to the position of plaintiffs, that is, those who are seeking to enforce trademark rights. After his usual scholarly review of the decisions, Prof. Derenberg concluded:

"If an attempt were made to summarzie the judicial approach expressed in the three last-mentioned Second Circuit cases, the conclusion would seem inescapable that an almost insuperable burden is now being placed upon those plaintiffs who seek legal protection against deliberate imitation by a competitor of nonfunctional features of their products."

Only 15 days after Prof. Derenberg's report went to press, the same court handed down the "Brylcreem" decision, thereby making the Professor appear to be a poor prophet, which he is not.

Perhaps the best explanation of the apparently conflicting "Pepto-Bismol" and "Brylcreem" decisions is that the *personnel* of the court underwent a change. This is believed to be quite close to the truth. Indeed, dissenting Judge Clark in the "Brylcreem" decision appears to say as much when, in referring to what he regards as a reversal of a line of recent decisions of the Second Circuit Court of Appeals, he states "that reversal comes because of the differing composition of the sitting panel."

It is unfortunate that such an important body of law as the question of how far business can go in developing trademarks and practices remains in such a precarious situation, with respect to inability to predict the outcome of litigation. However, in this

field of trademarks a certain and clear course which would avoid all difficulty is available: the late comer should set out to find a mark that differs materially from any of those in the field and should clothe his product in containers and with advertising that does not consciously imitate or closely approach what others already in the field do.

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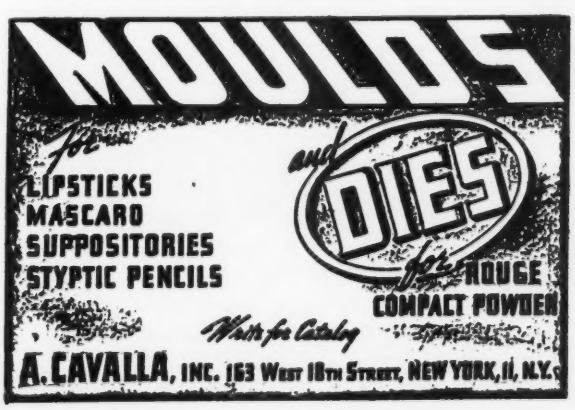

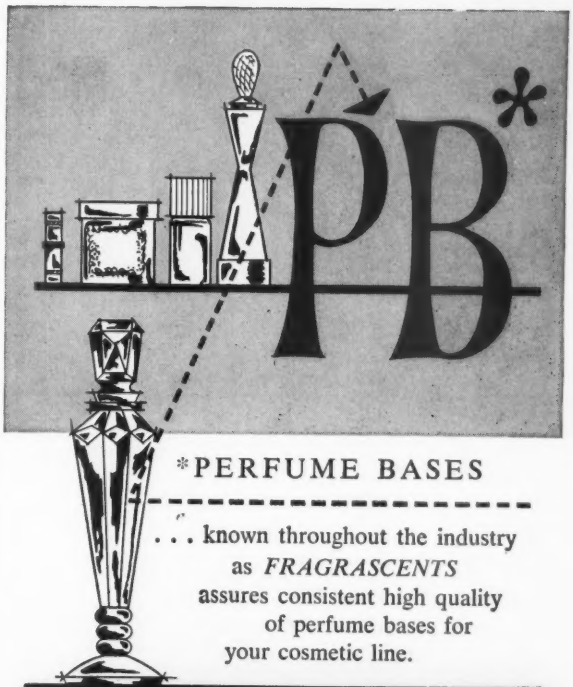

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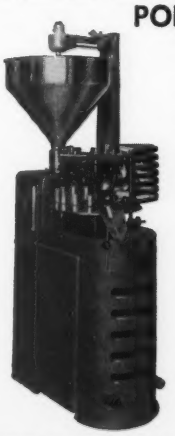

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